

Nucleic Acids, Proteins, and Antibodies

Statement under 37 C.F.R. § 1.77(b)(4)

- [001] This application refers to a "Sequence Listing" listed below, which is provided as an electronic document on two identical compact discs (CD-R), labeled "Copy 1" and "Copy 2." These compact discs each contain the file "PC009C1_seqList.txt" (4,095,326 bytes, created on March 6, 2002), which is hereby incorporated in its entirety herein.
- [002] The Sequence Listing may be viewed on an IBM-PC machine running the MS-Windows operating system.

Field of the Invention

- [003] The present invention relates to novel connective tissue related polynucleotides, the polypeptides encoded by these polynucleotides herein collectively referred to as "connective tissue antigens," and antibodies that immunospecifically bind these polypeptides, and the use of such connective tissue polynucleotides, antigens, and antibodies for detecting, treating, preventing and/or prognosing disorders of connective tissue(s), including, but not limited to, the presence of cancer and cancer metastases. More specifically, isolated connective tissue nucleic acid molecules are provided encoding novel connective tissue polypeptides. Novel connective tissue polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human connective tissue polynucleotides, polypeptides, and/or antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to connective tissue(s), including cancer, and therapeutic

methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The invention further relates to methods and/or compositions for inhibiting or promoting the production and/or function of the polypeptides of the invention.

Background of the Invention

[004] Connective tissues include those tissues that support and connect the various parts of the body. These tissues originate primarily in the cells of the mesodermal (middle tissue) layer of the embryo, and comprise the fibrous and elastic connective tissues, the adipose (fatty) tissues, and cartilage and bone. Connective tissues are composed of a variable structure of cells and fibers surrounded by an intercellular matrix that may be a fluid, solid, or gel, depending on the function of the particular connective tissue. White fibrous connective tissue forms most of the tendons and ligaments. Yellow elastic connective tissue forms such structures as the pads between the vertebrae and the elastic elements of the arterial walls and the trachea. Among other types of connective tissue, cartilage takes part in the formation of joints and the development of bone, and fat tissue provides a cushion for the support of such vital organs as the kidneys and stores excess food for use when needed. Lymphatic tissue and blood are also related in embryonic development to the connective tissues.

[005] Disorders that affect joints and their components--muscles, bones, cartilage, and tendons--are considered connective tissue diseases because these structures contain large amounts of connective tissue. However, many connective tissue diseases are also a type of autoimmune disease, involving immune reactions in which something triggers the immune system to react against the body's own tissues and to produce abnormal antibodies that attack these tissues (autoantibodies).

[006] Diseases of connective tissue may be due to genetic inheritance (such as, *e.g.*, Marfan syndrome, and Ehlers-Danlos syndrome); or alternatively may not have inheritance which can be defined by gene abnormalities (such as, *e.g.*, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, polymyositis, and dermatomyositis).

[007] A connective tissue disorder developing in about 1 percent of the population, Rheumatoid arthritis, is an autoimmune disease in which joints, usually including those of the hands and feet, are symmetrically inflamed, resulting in swelling, pain, and often the

eventual destruction of the joint's interior. Its exact cause isn't known, but many different factors, including genetic predisposition, may influence the autoimmune reaction. In this disease, the immune system attacks the tissue that lines and cushions joints. Eventually, the cartilage, bone, and ligaments of the joint erode, causing scars to form within the joint. The joints deteriorate at a highly variable rate. Rheumatoid arthritis may produce a low-grade fever and occasionally an inflammation of blood vessels (vasculitis) that causes nerve damage or leg sores (ulcers). Inflammation of the membranes around the lungs (pleurisy) or the sac surrounding the heart (pericarditis) or inflammation and scarring of the lungs can lead to chest pain, difficulty in breathing, and abnormal heart function. Some people develop swollen lymph nodes, Sjögren's syndrome, or an eye inflammation. Still's disease is a variation of rheumatoid arthritis in which high fever and other generalized symptoms develop first. Many people with rheumatoid arthritis have distinctive antibodies in their blood, for example, rheumatoid factor. Usually, the higher the level of rheumatoid factor in the blood, the more severe the rheumatoid arthritis and the poorer the prognosis.

[008] Psoriatic arthritis is a form of arthritis that occurs in people who have psoriasis of the skin or nails. The disease resembles rheumatoid arthritis but doesn't produce the antibodies characteristic of rheumatoid arthritis. Psoriasis (a skin condition causing flare-ups of red, scaly rashes and thickened, pitted nails) may precede or follow the joint inflammation. The arthritis usually affects joints of the fingers and toes, although other joints, including the hips and spine, are often affected as well. The joints may become swollen and deformed when inflammation is chronic. The skin and joint symptoms may appear and disappear together. The prognosis for psoriatic arthritis is usually better than that for rheumatoid arthritis because fewer joints are affected. Nonetheless, the joints can be severely damaged.

[009] A chronic, recurring disorder of unknown cause, discoid lupus erythematosus, is characterized by clearly defined round, red patches on the skin. The disorder is more common in females, most often women in their 30s. The characteristic rash may persist or may come and go for years and the appearance of the patches changes over time. Mouth sores are very common. If the disorder isn't treated, each patch gradually spreads outward. The central area degenerates, leaving a scar. In particularly scaly areas, the plugged hair follicles dilate, leaving pits shaped like carpet tacks. Scarring can cause widespread hair loss. The rash may be accompanied by achy joints and a decreased number of white blood

cells but is only infrequently accompanied by the more severe symptoms of systemic lupus erythematosus.

[010] Systemic lupus erythematosus (lupus) is an autoimmune disease that results in episodes of inflammation in joints, tendons, and other connective tissues and organs. Different tissues and organs become inflamed in different people, and the severity of the disease ranges from mild to debilitating, depending on the number and variety of antibodies that appear and the organs affected. About 90 percent of the people who have lupus are young women in their late teens to 30s, but children, mostly girls, and older men and women can also be affected. Occasionally, certain heart drugs (hydralazine, procainamide, and beta-blockers) can cause a lupus-like syndrome that disappears after the drug is discontinued. The number and variety of antibodies that can appear in lupus are greater than those in any other disease, and they, along with other unknown factors, determine which symptoms develop. Lupus can be quite mild, or it can be devastating, disabling, or fatal. Because symptoms vary greatly, lupus may resemble many other diseases. For example, the connective tissue of joints is commonly affected in lupus, and the arthritis that results may resemble rheumatoid arthritis. Lupus may resemble epilepsy or some psychologic disorders when the brain is affected. Although lupus can be chronic and ongoing, it usually flares up intermittently. What triggers a flare-up of lupus in people who are predisposed to it often isn't known, although sunlight seems to be one factor. About 90 percent of people with lupus have joint inflammation, which ranges from intermittent mild aches to severe arthritis in several joints. Years of joint symptoms may precede other symptoms. Long-standing joint inflammation can lead to deformity and permanent damage to the joint and surrounding tissue, but the bone doesn't erode as it does in rheumatoid arthritis.

[011] A chronic disease of unknown cause, Scleroderma (systemic sclerosis), is characterized by degenerative changes and scarring in the skin, joints, and internal organs and by blood vessel abnormalities. Fortunately, scleroderma is relatively rare. Approximately 300,000 people in the United States have the condition, which is more common in women, and those between the ages of 20 and 40. This disease is not contagious, nor is it inherited. Scleroderma results from an overproduction of collagen, the main supportive (connective tissue) protein in the body. While several theories exist as to why this occurs, no definitive cause has been established. Scleroderma may occur as part of mixed connective tissue disease. The usual initial symptoms are thickening and

swelling of the ends of the fingers. Raynaud's phenomenon, in which the fingers suddenly become very pale and tingle or become numb in response to cold or emotional upset, is also common. Aches and pains in several joints often accompany early symptoms. Heartburn, difficulty in swallowing, and shortness of breath are occasionally the first symptoms of scleroderma, but usually they appear later, if the esophagus, heart, and lungs become damaged.

[012] The CREST syndrome, also called limited cutaneous sclerosis (scleroderma), is usually a less severe form of the disease that's less likely to cause serious internal organ damage. The acronym CREST applies to the following manifestations: calcinosis (calcification in the skin); Raynaud's phenomenon (a sequence of color changes in the skin in response to cold); esophageal dysfunction (such as reflux or difficulty in swallowing); sclerodactyly (hardening of the skin of the fingers or toes); and telangiectasia (dilatation of tiny blood vessels, particularly of the skin). Skin damage is limited to the fingers. People who have the CREST syndrome can develop pulmonary hypertension, which can cause heart and respiratory failure. The course of scleroderma is variable and unpredictable. Sometimes scleroderma worsens rapidly and becomes fatal. At other times, it affects only the skin for decades before affecting internal organs, although some damage to internal organs such as the esophagus is almost inevitable, even in the CREST syndrome. The prognosis is worst for those who have early symptoms of heart, lung, or kidney damage. No drug can stop the progression of scleroderma.

[013] A chronic inflammatory disorder characterized by excessive dryness of the eyes, mouth, and other mucous membranes, is Sjögren's syndrome. This syndrome is often associated with other symptoms more characteristic of rheumatoid arthritis or systemic lupus erythematosus (lupus). Sjögren's syndrome is thought to be an autoimmune disease, but its cause isn't known. It's less common than rheumatoid arthritis and more prevalent in women than in men. Lymphoma, a cancer of the lymphatic system, is 44 times more common in people who have Sjögren's syndrome than in the general population. The prognosis depends on the potential of the antibodies to damage vital organs. Rarely, pneumonia, kidney failure, or lymphoma is fatal. No cure for Sjögren's syndrome is available, but symptoms can be relieved.

[014] Polymyositis is a chronic connective tissue disease characterized by painful inflammation and degeneration of the muscles; dermatomyositis is polymyositis accompanied by skin inflammation. These diseases result in disabling muscle weakness

and deterioration. The weakness typically occurs in the shoulders and hips but can affect muscles symmetrically throughout the body. Polymyositis and dermatomyositis usually occur in adults from ages 40 to 60 or in children from ages 5 to 15 years. Women are twice as likely as men to develop either disease. In adults, these diseases may occur alone or as part of other connective tissue diseases. The cause is unknown. Viruses or autoimmune reactions may play a role. Cancer may also trigger the diseases—an autoimmune reaction against cancer may be directed against a substance in the muscles as well. Symptoms, which may begin during or just after an infection, include muscle weakness (particularly in the upper arms, hips, and thighs), muscle and joint pain, Raynaud's phenomenon, a rash, difficulty in swallowing, a fever, fatigue, and weight loss. In dermatomyositis, rashes tend to appear at the same time as periods of muscle weakness and other symptoms.

[015] Mixed connective tissue disease is a collection of symptoms similar to those of several connective tissue diseases: systemic lupus erythematosus, scleroderma, polymyositis, and dermatomyositis. About 80 percent of the people who have this disease are women. It affects people from ages 5 to 80. Its cause is unknown, though an autoimmune reaction is likely. The typical symptoms are Raynaud's phenomenon (hands and feet that become white in spots and painful when chilled), joint aches or arthritis, swollen hands, muscle weakness, difficulty in swallowing, heartburn, and shortness of breath. Raynaud's phenomenon may precede other symptoms by many years. Regardless of how this disease starts, it tends to worsen, and symptoms spread to several parts of the body. Mixed connective tissue disease damages the muscle fibers, so the muscles may feel weak and sore, especially in the shoulders and hips. Although the esophagus is usually affected, it seldom causes difficulty in swallowing and isn't painful. Fluid may collect in or around the lungs. In some people, lung dysfunction is the most serious problem, causing shortness of breath during exertion and heart strain. Sjögren's syndrome may develop. Over time, most people develop symptoms that are more typical of lupus or scleroderma.

[016] Relapsing polychondritis is an uncommon disorder characterized by episodes of painful, destructive inflammation of the cartilage and other connective tissues in the ears, joints, nose, voice box (larynx), windpipe (trachea), bronchi, eyes, heart valves, kidneys, and blood vessels. This disorder affects men and women equally, usually in middle age.

[017] Vasculitis is an inflammation of blood vessels. Vasculitis is not a disease but rather a disease process that occurs in a number of autoimmune connective tissue diseases, such as rheumatoid arthritis and systemic lupus erythematosus. Vasculitis can also occur without connective tissue involvement. No one knows what triggers vasculitis in most people, but in some, hepatitis viruses are involved. Cells of the immune system, which cause inflammation, surround and infiltrate the affected blood vessels, destroying them and possibly damaging the tissues they supply. The blood vessels can become leaky or clogged; either condition disrupts blood flow to nerves, organs, and other parts of the body. Symptoms may result from direct damage to the blood vessels or damage to tissues whose blood supply is impaired. Vasculitis may be limited to veins, large arteries, small arteries, or capillaries, or it may be limited to vessels in one part of the body, such as the head, leg, or kidney. Disorders such as the Henoch-Schönlein syndrome, erythema nodosum, polyarteritis nodosa, temporal (giant cell) arteritis, and Takayasu's arteritis are characterized by vasculitis limited to blood vessels of a particular size or depth.

[018] Polyarteritis nodosa is a disease in which segments of medium-sized arteries become inflamed and damaged, reducing the blood supply to the organs they supply. This disease is often fatal if not treated adequately. It usually develops at 40 to 50 years of age but can occur at any age. Men are three times more likely than women to develop it. Its cause is unknown, but reactions to some drugs and vaccines may cause it. Viral and bacterial infections sometimes appear to trigger the inflammation, but most often no triggering event or substance can be found. The disease can be mild at first but fatal within several months, or it can develop subtly as a chronic debilitating disease.

[019] Connective tissue disorders further include, but are not limited to, Wegener's granulomatosis, an uncommon disease that often begins with an inflammation of the lining of the nose, sinuses, throat, or lungs and may progress to an inflammation of blood vessels throughout the body (generalized vasculitis) or fatal kidney disease; Reiter's syndrome, an inflammation of the joints and tendon attachments at the joints, often accompanied by an inflammation of the eye's conjunctiva and the mucous membranes, such as those of the mouth, urinary tract, vagina, and penis, and by a distinctive rash; Behçet's syndrome, a chronic, relapsing inflammatory disease that can produce recurring, painful mouth sores, skin blisters, genital sores, and swollen joints; and Ankylosing spondylitis, a disease characterized by an inflammation of the spine and large joints, resulting in stiffness and pain.

[020] Connective disorders can also involve the skin. For example, cellulitis, is an acute noncontagious inflammation of the connective tissue of the skin, resulting from Staphylococcus, Streptococcus, or other bacterial infection. Keloids develop from an overgrowth of scar tissue at the site of a skin injury.

[021] Ehler Danlos syndrome is one of the inheritable connective tissues disorders along with: Marfan syndrome, pseudoxantoma elasticum, osteogenese imperfecta, chondrodysplasias, epidermolysis bullosa and Alport syndrome. It comprises a group of ten different subtypes. The main clinical manifestations are skin fragility, abnormal scar formation, excessive bruising, joint laxity and sometimes rupture of viscera and arteries. The basic defect is in the synthesis of collagen type I and III, leading to low tensile strength of skin and artery wall.

[022] Cutis laxa is a rare, inherited or acquired connective tissue disorder in which skin becomes inelastic and hangs loosely in folds. Clinical presentation and the mode of inheritance show considerable heterogeneity; and autosomal dominant, autosomal recessive, and X-linked recessive patterns have been noted in inherited forms. The precise cause is unknown, but may be due to abnormal elastin metabolism resulting in markedly reduced dermal elastin content.

[023] The discovery of new human connective tissue associated polynucleotides, the polypeptides encoded by them, and antibodies that immunospecifically bind these polypeptides, satisfies a need in the art by providing new compositions which are useful in the diagnosis, treatment, prevention and/or prognosis of disorders of connective tissues, including, but not limited to, rheumatoid arthritis, psoriatic arthritis, discoid lupus erythematosus, systemic lupus erythematosus, scleroderma, CREST syndrome, Sjogren's syndrome, polymyositis, dermatomyositis, mixed connective tissue disease, relapsing polychondritis, vasculitis, Henoch-Schonlein syndrome, erythema nodosum, polyarteritis nodosa, temporal (giant cell) arteritis, Takayasu's arteritis, Wegener's granulomatosis, Reiter's syndrome, Behcet's syndrome, ankylosing spondylitis, cellulitis, keloids, Ehler Danlos syndrome, Marfan syndrome, pseudoxantoma elasticum, osteogenese imperfecta, chondrodysplasias, epidermolysis bullosa, Alport syndrome, cutis laxa, genetic disorders affecting skeleton, skin and muscles; formation of excessive scar tissue; deposition of pathological amounts of connective tissue in body organs, including kidney, intestines and heart, and in liver by liver cirrhosis, in skin by scleroderma, in lung by lung fibrosis,

in bone marrow by leukemia, in blood vessels by atherosclerosis, and in joints by rheumatic diseases.

Summary of the Invention

[024] The present invention relates to novel connective tissue related polynucleotides, the polypeptides encoded by these polynucleotides herein collectively referred to as "connective tissue antigens," and antibodies that immunospecifically bind these polypeptides, and the use of such connective tissue polynucleotides, antigens, and antibodies for detecting, treating, preventing and/or prognosing disorders of the connective tissue, including, but not limited to, the presence of cancer and cancer metastases. More specifically, isolated connective tissue nucleic acid molecules are provided encoding novel connective tissue polypeptides. Novel connective tissue polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human connective tissue polynucleotides, polypeptides, and/or antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to connective tissue, including cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The invention further relates to methods and/or compositions for inhibiting or promoting the production and/or function of the polypeptides of the invention.

Detailed Description

Tables

[025] Table 1A summarizes some of the polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID NO:Z), contig sequences (contig identifier (Contig ID:)) and contig nucleotide sequence identifier (SEQ ID NO:X)) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby. The first column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA plasmid related to each connective tissue associated contig sequence disclosed in Table 1A. The second column provides a unique contig identifier,

"Contig ID:" for each of the contig sequences disclosed in Table 1A. The third column provides the sequence identifier, "SEQ ID NO:X", for each of the contig polynucleotide sequences disclosed in Table 1A. The fourth column, "ORF (From-To)", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:X that delineate the preferred open reading frame (ORF) shown in the sequence listing and referenced in Table 1A as SEQ ID NO:Y (column 5). Column 6 lists residues comprising predicted epitopes contained in the polypeptides encoded by each of the preferred ORFs (SEQ ID NO:Y). Identification of potential immunogenic regions was performed according to the method of Jameson and Wolf (CABIOS, 4:181-186 (1988)); specifically, the Genetics Computer Group (GCG) implementation of this algorithm, embodied in the program PEPTIDESTRUCTURE (Wisconsin Package v10.0, Genetics Computer Group (GCG), Madison, Wisc.). This method returns a measure of the probability that a given residue is found on the surface of the protein. Regions where the antigenic index score is greater than 0.9 over at least 6 amino acids are indicated in Table 1A as "Predicted Epitopes." In particular embodiments, connective tissue associated polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the predicted epitopes described in Table 1A. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. Column 7, "Tissue Distribution" shows the expression profile of tissue, cells, and/or cell line libraries which express the polynucleotides of the invention. The first number in column 7 (preceding the colon), represents the tissue/cell source identifier code corresponding to the code and description provided in Table 4. Expression of these polynucleotides was not observed in the other tissues and/or cell libraries tested. For those identifier codes in which the first two letters are not "AR", the second number in column 7 (following the colon), represents the number of times a sequence corresponding to the reference polynucleotide sequence (e.g., SEQ ID NO:X) was identified in the tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array. cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of ³³P dCTP, using oligo(dT) to prime

reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after "[array code]:" represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression. Column 8, "Cytologic Band," provides the chromosomal location of polynucleotides corresponding to SEQ ID NO:X. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Given a presumptive chromosomal location, disease locus association was determined by comparison with the Morbid Map, derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM™. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>). If the putative chromosomal location of the Query overlapped with the chromosomal location of a Morbid Map entry, an OMIM identification number is provided in Table 1A, column 9 labeled "OMIM Disease Reference(s)". A key to the OMIM reference identification numbers is provided in Table 5.

[026] Table 2 summarizes homology and features of some of the polypeptides of the invention. The first column provides a unique clone identifier, "Clone ID NO:Z", corresponding to a cDNA disclosed in Table 1A. The second column provides the unique contig identifier, "Contig ID:" corresponding to contigs in Table 1A and allowing for correlation with the information in Table 1A. The third column provides the sequence identifier, "SEQ ID NO:X", for the contig polynucleotide sequences. The fourth column provides the analysis method by which the homology/identity disclosed in the row was

determined. Comparisons were made between polypeptides encoded by the polynucleotides of the invention and either a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFAM") as further described below. The fifth column provides a description of PFAM/NR hits having significant matches to a polypeptide of the invention. Column six provides the accession number of the PFAM/NR hit disclosed in the fifth column. Column seven, "Score/Percent Identity", provides a quality score or the percent identity, of the hit disclosed in column five. Columns 8 and 9, "NT From" and "NT To" respectively, delineate the polynucleotides in "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFAM/NR database as disclosed in the fifth column. In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence encoded by the polynucleotides in SEQ ID NO:X as delineated in columns 8 and 9, or fragments or variants thereof.

[027] Table 3 provides polynucleotide sequences that may be disclaimed according to certain embodiments of the invention. The first column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA clone related to connective tissue associated contig sequences disclosed in Table 1A. The second column provides the sequence identifier, "SEQ ID NO:X", for contig polynucleotide sequences disclosed in Table 1A. The third column provides the unique contig identifier, "Contig ID", for contigs disclosed in Table 1A. The fourth column provides a unique integer 'a' where 'a' is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, represented as "Range of a", and the fifth column provides a unique integer 'b' where 'b' is any integer between 15 and the final nucleotide of SEQ ID NO:X, represented as "Range of b", where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. For each of the polynucleotides shown as SEQ ID NO:X, the uniquely defined integers can be substituted into the general formula of a-b, and used to describe polynucleotides which may be preferably excluded from the invention. In certain embodiments, preferably excluded from the polynucleotides of the invention (including polynucleotide fragments and variants as described herein and diagnostic and/or therapeutic uses based on these polynucleotides) are at least one, two, three, four, five, ten, or more of the polynucleotide sequence(s) having the accession number(s) disclosed in the sixth column of this Table (including for example, published sequence in connection with a particular BAC clone). In further embodiments, preferably

excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table (including for example, the actual sequence contained in an identified BAC clone).

[028] Table 4 provides a key to the tissue/cell source identifier code disclosed in Table 1A, column 7. Column 1 provides the key to the tissue/cell source identifier code disclosed in Table 1A, Column 7. Columns 2-5 provide a description of the tissue or cell source. Codes corresponding to diseased tissues are indicated in column 6 with the word "disease". The use of the word "disease" in column 6 is non-limiting. The tissue or cell source may be specific (e.g. a neoplasm), or may be disease-associated (e.g., a tissue sample from a normal portion of a diseased organ). Furthermore, tissues and/or cells lacking the "disease" designation may still be derived from sources directly or indirectly involved in a disease state or disorder, and therefore may have a further utility in that disease state or disorder. In numerous cases where the tissue/cell source is a library, column 7 identifies the vector used to generate the library.

[029] Table 5 provides a key to the OMIM™ reference identification numbers disclosed in Table 1A, column 9. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM™. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine, (Bethesda, MD) 2000. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>). Column 2 provides diseases associated with the cytologic band disclosed in Table 1A, column 8, as determined from the Morbid Map database.

[030] Table 6 summarizes ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application.

[031] Table 7 shows the cDNA libraries sequenced, tissue source description, vector information and ATCC designation numbers relating to these cDNA libraries.

[032] Table 8 provides a physical characterization of clones encompassed by the invention. The first column provides the unique clone identifier, "Clone ID NO:Z", for certain cDNA clones of the invention, as described in Table 1A. The second column provides the size of the cDNA insert contained in the corresponding cDNA clone.

Definitions

[033] The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

[034] In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide sequences of the present invention.

[035] As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence encoding SEQ ID NO:Y or a fragment or variant thereof, a nucleic acid sequence contained in SEQ ID NO:X (as described in column 3 of Table 1A) or the complement thereof, a cDNA sequence contained in Clone ID NO:Z (as described in column 1 of Table 1A and contained within a library deposited with the ATCC); a nucleotide sequence encoding the polypeptide encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B or a fragment or variant thereof; or a nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complement thereof. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

[036] As used herein, a "connective tissue antigen" refers collectively to any polynucleotide disclosed herein (e.g., a nucleic acid sequence contained in SEQ ID NO:X or the complement thereof, or cDNA sequence contained in Clone ID NO:Z, or a nucleotide sequence encoding the polypeptide encoded by a nucleotide sequence in SEQ

ID NO:B as defined in column 6 of Table 1B, or a nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complement thereof and fragments or variants thereof as described herein) or any polypeptide disclosed herein (e.g., an amino acid sequence contained in SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, or the complement thereof, an amino acid sequence encoded by the cDNA sequence contained in Clone ID NO:Z, an amino acid sequence encoded by SEQ ID NO:B, or the complement thereof, and fragments or variants thereof as described herein). These connective tissue antigens have been determined to be predominantly expressed in connective tissues, including normal or diseased tissues (as shown in Table 1A column 7 and Table 4).

[037] In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown, for example, in column 1 of Table 1A, each clone is identified by a cDNA Clone ID (identifier generally referred to herein as Clone ID NO:Z). Each Clone ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. Furthermore, certain clones disclosed in this application have been deposited with the ATCC on October 5, 2000, having the ATCC designation numbers PTA 2574 and PTA 2575; and on January 5, 2001, having the depositor reference numbers TS-1, TS-2, AC-1, and AC-2. In addition to the individual cDNA clone deposits, most of the cDNA libraries from which the clones were derived were deposited at the American Type Culture Collection (hereinafter "ATCC"). Table 7 provides a list of the deposited cDNA libraries. One can use the Clone ID NO:Z to determine the library source by reference to Tables 6 and 7. Table 7 lists the deposited cDNA libraries by name and links each library to an ATCC Deposit. Library names contain four characters, for example, "HTWE." The name of a cDNA clone (Clone ID NO:Z) isolated from that library begins with the same four characters, for example "HTWEP07". As mentioned below, Table 1A correlates the Clone ID NO:Z names with SEQ ID NO:X. Thus, starting with an SEQ ID NO:X, one can use Tables 1A, 6 and 7 to determine the corresponding Clone ID NO:Z, which library it came from and which ATCC deposit the library is contained in. Furthermore, it is possible to retrieve a given cDNA clone from the source library by techniques known in the art and described elsewhere herein. The ATCC is located at 10801 University

Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[038] In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5 kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

[039] A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), the polynucleotide sequence delineated in columns 8 and 9 of Table 2 or the complement thereof, and/or cDNA sequences contained in Clone ID NO:Z (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments, or the cDNA clone within the pool of cDNA clones deposited with the ATCC, described herein) and/or the polynucleotide sequence delineated in column 6 of Table 1B or the complement thereof. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

[040] Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency), salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution

comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH₂PO₄; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

[041] Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

[042] Of course, a polynucleotide which hybridizes only to polyA⁺ sequences (such as any 3' terminal polyA⁺ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

[043] The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

[044] The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may

contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992).)

[045] "SEQ ID NO:X" refers to a polynucleotide sequence described, for example, in Tables 1A or 2, while "SEQ ID NO:Y" refers to a polypeptide sequence described in column 5 of Table 1A. SEQ ID NO:X is identified by an integer specified in column 3 of Table 1A. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. "Clone ID NO:Z" refers to a cDNA clone described in column 1 of Table 1A.

[046] "A polypeptide having biological activity" refers to a polypeptide exhibiting activity similar to, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

[047] Table 1A summarizes some of the polynucleotides encompassed by the invention (including contig sequences (SEQ ID NO:X) and clones (Clone ID NO:Z) and further summarizes certain characteristics of these polynucleotides and the polypeptides encoded thereby.

Polynucleotides and Polypeptides

TABLE 1A

Clone ID NO: Z	Contig ID:	SEQ ID NO: X	ORF (From-To)	AA SEQ ID NO: Y	Predicted Epitopes	Tissue Distribution Library code: count (see Table IV for Library Codes)	Cytologic Band	OMIM Disease Reference(s):
HABGB54	952557	11	1 - 156	500		S0348: 5		
HACAD23	926345	12	3 - 341	501	Gln-25 to Lys-30.	AR050: 11, AR054: 11, AR051: 10 H0593: 2, S6022: 1, L0435: 1 and L0438: 1.		
	926346	492	1 - 213	981	Gly-1 to Ala-6.			
HACAI48	575814	13	3 - 200	502		S6022: 2		
HACBA49	722875	14	253 - 426	503	Ser-11 to Gly-16, Gln-21 to Ser-26.	S0280: 2		
HACBT81	855720	15	75 - 323	504	Gly-20 to Asp-30, Ser-36 to Gly-59.	S0280: 2		
HACCY20	845144	16	15 - 356	505		S0280: 3		
HADAM37	731696	17	161 - 319	506	Ser-6 to Asn-16.	H0427: 2		
HADAM69	699190	18	198 - 353	507	Ile-1 to Pro-7, Lys-28 to Thr-33.	H0427: 2		
HADAR35	705743	19	3 - 158	508	Gly-32 to Thr-42.	H0427: 3		
HADCK83	609846	20	172 - 540	509	Phe-9 to Lys-14, Ser-87 to Ile-93, Lys-113 to His-123.	H0427: 2		
	883471	493	196 - 2	982	Arg-10 to Asn-19, Pro-25 to Phe-31, Asn-35 to Phe-48.			
HADCL22	674427	21	182 - 334	510	Cys-20 to Lys-28, Cys-36 to Gly-41.	L0769: 4 and H0427: 2.		
HADCO14	657572	22	61 - 288	511	Lys-1 to Leu-8,	H0427: 2		

						Lys-25 to Gly-32, Pro-62 to Gly-71.			
HADCO44	716559	23	65 - 202	512				H0427: 2	
HADCO48	865306	24	13 - 183	513		Asn-14 to Val-19.		H0427: 2	
HADCO54	467197	25	198 - 368	514		Val-15 to Glu-27.		H0427: 2	
HADCO57	734705	26	1 - 147	515				H0427: 2	
HADCQ37	970564	27	2 - 556	516				H0427: 2 and H0600: 1.	
HADCU18	666360	28	2 - 448	517		His-9 to Pro-15, Met-34 to Gln-39, Pro-68 to Arg-73, Lys-105 to Gln-118, Gln-130 to Ala-135.		H0427: 2	
HADCW65	719810	29	111 - 272	518				H0427: 2	
HADCX38	705751	30	161 - 325	519		Arg-13 to Leu-20.		H0427: 2	
HADDB75	757028	31	188 - 433	520		Asn-69 to Gly-81.		H0587: 1 and H0427: 1.	
HADD66	787301	32	303 - 485	521		Lys-28 to Arg-34.		H0427: 2	
HADDE78	773552	33	131 - 319	522		Phe-36 to Ser-43.		H0427: 2	
HADDF89	786876	34	1 - 165	523		Thr-12 to Cys-21, Glu-28 to Glu-39.		H0427: 2	
HADDQ25	849002	35	129 - 386	524		Arg-1 to Cys-8, Cys-28 to Arg-34.		H0427: 2	
HADEU56	733346	36	300 - 473	525		Pro-47 to Asn-55.		H0427: 2	
HADFG58	727536	37	8 - 187	526		Arg-1 to Gln-6, Thr-26 to Glu-31, Arg-52 to Lys-58.		H0427: 2	
HADFX30	970565	38	1 - 420	527		Arg-1 to Pro-8.		H0427: 3	
HADFX35	675830	39	154 - 360	528		Thr-35 to Asn-44.		H0427: 2	

HADGA36	705766	40	3 - 155	529	Ser-23 to Gly-30.	H0427: 2 and L0662: 1.		
HADGD54	729761	41	1 - 183	530	Pro-9 to Pro-14.	T0060: 1 and H0427: 1.		
HADGE37	744768	42	1 - 261	531		H0600: 1 and H0427: 1.		
HADGR61	848971	43	210 - 467	532	Pro-13 to Ser-18.	H0427: 3		
HADXA61	741926	44	204 - 302	533	Gln-27 to Gly-32.	H0443: 2		
HARMG09	705996	45	49 - 222	534		H0592: 2		
HARMG60	933284	46	1 - 165	535		H0592: 2		
HARMM43	714763	47	3 - 251	536		H0592: 2		
HARMP39	705255	48	329 - 598	537	Asn-1 to Tyr-7.	H0592: 2		
HARMP42	713247	49	292 - 453	538		H0592: 2		
HARMS39	933273	50	3 - 494	539	Ser-1 to Leu-11, Ser-67 to Phe-73, Ser-112 to Ser-120.	H0592: 1 and H0587: 1.		
HARMS77	752659	51	2 - 184	540		H0592: 2		
HARMU03	923179	52	41 - 145	541		H0592: 2		
HARMX01	915475	53	131 - 394	542	Asn-18 to Arg-25, Ile-48 to Ala-53, Gln-78 to Thr-84.	H0592: 2, L0385: 1 and L0731: 1.		
HARMX35	759963	54	3 - 284	543	Lys-1 to Pro-6, Lys-8 to Lys-15, Phe-33 to Ile-40, Asn-50 to Glut-58.	H0592: 2		
HARNC40	710613	55	143 - 268	544	Ser-21 to Gly-28.	H0592: 2		
HARND80	864604	56	3 - 623	545	Phe-47 to Val-57, Leu-68 to Asn-78, Trp-104 to Gly-110.	H0592: 1, H0586: 1 and L0749: 1.		

HARNH15	687972	57	374 - 568	546	Tyr-2 to Pro-7, Cys-11 to Ser-16.	H0592: 2		
HARNH52	726277	58	1 - 132	547		H0592: 2		
HARNO29	690043	59	392 - 219	548		H0592: 2		
HAWAD93	508724	60	2 - 190	549	Thr-1 to Trp-7.	T0060: 2		
HAWAP49	537199	61	226 - 375	550		H0587: 1, T0060: 1, T0004: 1, L0667: 1 and L0750: 1.		
HBIMG05	930827	62	3 - 518	551		H0494: 1 and H0593: 1.		
HBIMS01	913827	63	379 - 570	552		H0494: 1 and H0593: 1.		
HBIOO63	969020	64	1 - 261	553	Gly-1 to Gly-6, His-23 to Gly-28, Ser-41 to Leu-51, Thr-53 to Ser-65.	H0593: 2		
HBIOP02	918022	65	28 - 111	554		H0593: 2		
HBIO505	930776	66	3 - 437	555	Met-44 to Gly-49, Gln-105 to Gln-120.	AR089: 4, AR061: 2 H0593: 4		
HBIOX83	965609	67	55 - 315	556	Thr-8 to Val-19, Arg-62 to Thr-76.	H0593: 4 and H0023: 1.		
HERAC86	973654	68	416 - 685	557	Pro-1 to Phe-14, Ala-25 to Arg-31, Glu-44 to Gln-49.	H0345: 2		
HERAC92	973454	69	225 - 422	558	Asn-8 to Lys-24, Ala-45 to Phe-53.	H0345: 2		
HERAD04	927788	70	109 - 300	559		H0345: 2		
HERAD10	973489	71	228 - 374	560	His-1 to Ser-17, Ser-29 to Gly-38.	H0345: 2		

HERAD21	954708	72	2 - 268	561	Ala-1 to Gln-17, Pro-56 to Thr-62.	H0345: 2	
HERAG57	973668	73	50 - 196	562	Ser-1 to Trp-7, Tyr-17 to Ser-22.	H0345: 2	
HERAJ78	973676	74	392 - 589	563		H0345: 2	
HERAL93	974497	75	250 - 534	564	Lys-1 to Cys-17.	H0345: 2	
HERAM84	529193	76	1 - 180	565	Thr-6 to Gly-12, Ala-42 to Arg-48.	H0345: 2	
HERAN13	973709	77	360 - 542	566	Lys-32 to Lys-37, Gln-46 to Asn-51.	H0345: 2	
HERAR12	735275	78	240 - 326	567		H0345: 2	
HESAD92	537451	79	229 - 381	568		H0086: 2	
HESAT22	537449	80	110 - 352	569	Arg-1 to Lys-14, Pro-19 to Gly-29, Glu-32 to Glu-60.	H0086: 2	
HESAT88	537446	81	136 - 222	570		H0086: 2	
HFEAG37	705454	82	89 - 193	571	Leu-5 to Val-12, Ala-23 to Gly-34.	H0081: 2	
HFEAH35	504585	83	74 - 259	572	Ala-1 to Thr-7.	H0081: 2	
HFEAN02	932828	84	51 - 209	573		H0081: 2	
HFEAN43	524355	85	2 - 163	574		H0081: 2	
HFEAO67	954402	86	3 - 344	575		H0081: 2	
HFEAQ11	530368	87	93 - 242	576	Gly-7 to His-17.	H0081: 2	
HFEAS89	960624	88	52 - 309	577		H0081: 2	
HFEBB19	974533	89	56 - 328	578	Gly-1 to Glu-7, Gly-15 to Gly-24, Gln-31 to Gly-41.	H0081: 2	
HFEBB35	974535	90	1 - 336	579	Gly-1 to His-9, Ser-28 to Ser-34.	H0081: 2	

							Leu-68 to Met-74, Ser-81 to Trp-87.				
HFEBD62	789763	91	210 - 398	580			Asp-1 to Ser-7, Ala-19 to Phe-27, Asn-40 to Asn-46.		H0081: 1 and H0494: 1.		
HFEBF21	974270	92	237 - 596	581			Gly-5 to Gly-14, Glu-21 to Asp-27, Asp-34 to Cys-39, Asn-77 to Pro-83, Gly-109 to Arg-118.		H0081: 3		
HFEBG06	935683	93	251 - 412	582					H0081: 2		
HFEBL88	766085	94	12 - 359	583					H0586: 1 and H0081: 1.		
HFJAA51	725626	95	1 - 51	584			Glu-1 to Gly-7.		H0548: 2		
HFJAA62	855107	96	1 - 330	585					H0548: 2		
HKAAU11	966953	97	155 - 430	586			Leu-4 to Asn-11, Tyr-33 to Ala-39.		H0586: 1 and H0494: 1.		
HKABE64	879492	98	242 - 493	587			Ala-1 to Ala-14.		H0494: 2		
HKABR48	702372	99	1 - 504	588			Pro-15 to Gly-21, Arg-30 to Leu-42, Arg-93 to Gln-99, Thr-102 to Gly-108, Asp-116 to Thr-121.		H0494: 2, L0751: 2, L0806: 1, L0789: 1 and L0780: 1.		
HKACB30	466848	100	290 - 469	589			Arg-1 to Tyr-20.		L0754: 2, H0586: 1 and H0494: 1.		
HKACG80	750256	101	3 - 173	590			Pro-1 to Asn-17, Pro-36 to Thr-45, Glu-47 to Tyr-52.		H0494: 2		
HKACL95	973360	102	1 - 396	591					H0494: 2		

[illegible]

HKACM63	952653	103	101 - 352	592	Ser-32 to Gly-38.	H0587: 1 and H0494: 1.		
HKACU93	908022	104	2 - 484	593	Leu-2 to Pro-9, Arg-14 to His-20, Arg-26 to Thr-32, Met-66 to Thr-75, Leu-77 to Lys-82.	H0494: 2, L0794: 1 and L0743: 1.		
HKACY54	862787	105	36 - 269	594	Arg-18 to Leu-31, Leu-56 to Trp-70.	H0494: 2	11q13	102200, 106100, 131100, 131100, 131100, 131100, 133780, 147050, 153700, 161015, 164009, 168461, 168461, 168461, 180721, 180840, 191181, 193235, 209901, 232600, 259700, 259770, 600045, 600319,

												600528, 601884
HKADC82	944994	106	155 - 529	595	Glu-1 to Ser-9, Asp-38 to Asn-45.				AR089: 2, AR061: 1 L0766: 5, H0494: 2, L0755: 2, L0800: 1, L0773: 1 and L0777: 1.			
	951091	494	370 - 194	983	Gln-39 to Ser-44.							
HKADP74	765535	107	36 - 470	596	Thr-1 to Gly-7, Pro-31 to Met-40, Asn-56 to Pro-62.				H0494: 2 and L0749: 1.		17	
HKAEC04	857355	108	139 - 351	597	Asp-1 to Gly-13.				H0494: 2 and L0758: 1.			
HKAE60	812691	109	1 - 147	598	Arg-18 to Glu-25, Gly-37 to Ser-42.				H0081: 1 and H0494: 1.			
HKAEP23	672808	110	2 - 250	599	Gly-3 to Arg-8.				H0592: 1 and H0494: 1.			
HKADEV94	973353	111	3 - 338	600	Thr-1 to Gly-6, Pro-20 to Pro-35.				H0494: 2			
HKAFI36	930711	112	169 - 2	601	Glu-45 to Lys-56.				S6022: 1, H0494: 1, L0662: 1 and L0608: 1.			
HKAFO42	713722	113	94 - 252	602					H0427: 1 and H0494: 1.			
HKAFFZ12	970570	114	34 - 255	603					H0494: 2			
HKAH84	887386	115	3 - 332	604					AR050: 40, AR054: 33, AR051: 33 S0040: 1 and H0494: 1. H0494: 2			
HKAHI83	780669	116	2 - 220	605					H0494: 2			
HKAHT29	958404	117	1 - 57	606	Phe-11 to Met-19.				H0494: 2			
HKAIF25	974416	118	43 - 225	607					H0494: 2			

HKAIL12	893937	119	2 - 301	608	Pro-1 to Thr-10, Pro-45 to Gly-70, Pro-72 to Gly-78.	H0494: 2 and H0593: 1.		
HKAJU82	779322	120	2 - 514	609	Ser-15 to Ser-28, Phe-36 to Gly-42, Asp-49 to Ser-58, Gly-65 to Pro-89, Arg-115 to Gly-122.	H0494: 4		
HKAJG02	857330	121	260 - 394	610		H0427: 1, H0494: 1, L0520: 1, L0388: 1 and L0750: 1.		
HKAJR01	915313	122	94 - 279	611		H0494: 5		
HKAJW52	836587	123	1 - 171	612	Gly-27 to Gly-32.	H0494: 2		
HKAKI80	973231	124	282 - 512	613	Arg-13 to Tyr-20.	H0494: 3		
HKAKL94	782287	125	3 - 95	614	Pro-14 to Lys-23.	H0494: 2		
HKAKP85	927032	126	2 - 145	615		H0494: 3		
HKAOE10	963543	127	157 - 312	616		T0004: 1, H0494: 1, L0794: 1, L0766: 1 and L0439: 1.		
HKAOM71	761303	128	8 - 310	617	Asn-44 to Ser-56, Asn-62 to Lys-68.	H0494: 2		
HKAON82	779247	129	1 - 327	618		H0494: 2		
HKAOU93	791779	130	113 - 388	619	Gly-33 to Gly-39.	L0754: 3, H0494: 2, L0747: 2, H0586: 1, L0598: 1, L0800: 1, L0791: 1, L0779: 1 and L0777: 1.		
HKAPN78	973220	131	206 - 457	620	Pro-8 to Ser-23, Val-25 to Gly-31.	H0494: 2		

HOUAT14	527920	132	190 - 333	621			S0040: 2		
HOUBL71	527805	133	146 - 301	622			S0040: 2		
HOUCL76	531425	134	73 - 144	623			S0040: 2		
HOUER21	936034	135	1 - 315	624		Gly-1 to Gln-6, Arg-20 to Pro-28, Gly-59 to Val-68, Thr-82 to Gly-95, Ser-98 to Pro-105.	S0040: 2		
HOUER26	573977	136	79 - 246	625		Val-15 to Ser-21.	S0040: 2	19q	
HOUER27	682162	137	113 - 352	626		Glu-1 to Cys-6.	S0040: 2		
HOUER91	526717	138	3 - 182	627			S0040: 3		
HOUER46	719181	139	136 - 309	628			S0040: 2		
HOUER40	573873	140	9 - 215	629			S0040: 2		
HOUER50	724607	141	1 - 72	630			S0040: 2		
HOUER25	524248	142	1 - 159	631		Glu-1 to Leu-6, Arg-22 to Asn-27, Tyr-36 to Ser-43.	S0040: 2		
HOUER50	573874	143	1 - 159	632		Tyr-6 to Ser-18.	S0040: 2		
HOUER87	837251	144	1023 - 772	633		Lys-52 to Gly-60, Ala-67 to Glu-79.	AR051: 31, AR054: 27, AR050: 23 S0040: 2		
	838457	495	277 - 528	984		Lys-52 to Gly-60, Ala-67 to Glu-79.			
HOUERQ33	701762	145	31 - 246	634		Cys-3 to Ser-8.	S0040: 2		
HOUER79	774089	146	3 - 227	635		Cys-1 to Lys-14.	S0040: 2		
HOUERV24	676834	147	57 - 176	636			S0040: 2		
HOUERV31	697592	148	165 - 521	637		Lys-1 to Ser-8.	S0040: 2		
HOUERV52	840297	149	248 - 430	638		Ser-1 to Lys-13, Pro-19 to Asp-26.	S0040: 2		

HOUFW07	952632	150	15 - 197	639	Trp-19 to His-24, His-39 to Ser-45.	S0040: 2	
HOUFZ64	750784	151	3 - 161	640		S0040: 2	
HOUGD02	915761	152	3 - 74	641		S0040: 2	
HOUGD13	656607	153	12 - 236	642	Lys-7 to Phe-12.	S0040: 2	
HOUHU87	791044	154	100 - 234	643	Asn-26 to Pro-33.	S0342: 2	
HSTAE16	827112	155	3 - 281	644	Gly-58 to Thr-65, Ser-72 to Glu-78.	H0068: 3	
HSTAE32	508961	156	122 - 262	645		H0068: 2	
HSTAE39	584942	157	123 - 275	646	Pro-4 to Pro-10.	H0068: 2	2
HSTAH26	861435	158	294 - 100	647		H0068: 2	
HSTAL08	960473	159	18 - 290	648		H0068: 4	
HSTAL23	508812	160	66 - 149	649		H0068: 2	
HSTAL64	508813	161	241 - 336	650		H0068: 3 and L0664: 1.	
HSTAL92	508820	162	112 - 273	651		H0068: 2	
HSTAO16	508808	163	174 - 359	652	Thr-12 to Ser-17, Ser-40 to Arg-50.	H0068: 2	
HSTAP23	508802	164	218 - 337	653	Asn-1 to Lys-18.	H0068: 2	
HSTAP31	508803	165	2 - 136	654		H0068: 3	
HSTAP89	508805	166	51 - 209	655	Phe-1 to Asn-6.	H0068: 3	
HSTAQ54	968671	167	167 - 292	656	Tyr-1 to Gly-9.	H0068: 4	
HSTAQ67	508800	168	54 - 335	657	Gly-10 to Gly-16, Ser-26 to Trp-34, Ser-45 to Gly-54, Lys-68 to Tyr-76, Lys-81 to Gly-87.	H0068: 2	
HSTAX16	508960	169	2 - 103	658	Thr-15 to Leu-21.	H0068: 2	
HSTAX68	508797	170	135 - 1	659		H0068: 2	

HSTAZ54	508368	171	1 - 336	660			H0068: 2			
HSTBC04	506961	172	2 - 289	661		Ser-7 to Leu-23.	H0068: 2	19p13.3	108725, 120700, 133171, 136836, 145981, 147141, 164953, 188070, 600957, 601238, 601846, 602216, 602477	
HSTBJ41	526608	173	113 - 211	662		Leu-9 to Arg-19.	H0068: 2			
HWDAC04	927471	174	112 - 339	663		His-12 to Tyr-18, Val-51 to Pro-58.	H0600: 2			
HWDAC71	752776	175	26 - 136	664			H0600: 2			
HWDAG13	746132	176	213 - 368	665			H0600: 2			
HWDAN69	676671	177	269 - 586	666		Glu-15 to Glu-22, Gln-33 to Gly-40.	H0600: 2			
HWDAO04	927231	178	101 - 223	667			H0600: 2 and L0776: 1.			
HWDAO26	679520	179	2 - 448	668		Cys-17 to Ser-24.	H0600: 1 and H0587: 1.			
HWDAP03	923319	180	184 - 372	669		Arg-1 to Trp-9.	H0600: 1 and H0593: 1.			
HWDAS34	703610	181	24 - 425	670		Pro-7 to Gly-15, Ala-41 to Gly-48, Val-65 to Ala-71.	L0751: 4 and H0600: 2.			

HWDAS64	729159	182	189 - 494	671	Gly-1 to Val-19, Asp-43 to Leu-48.	AR061: 2, AR089: 1 H0600: 1 and H0587: 1.		
HWDAS93	707809	183	1 - 123	672		H0600: 2		
HWEAD11	965030	184	2 - 310	673		H0601: 2		
HWHGB20	669455	185	265 - 501	674	Asp-1 to Ala-6, Pro-12 to Arg-18, Thr-46 to Gly-58, Thr-74 to His-79.	H0586: 2		
HWHGB21	954002	186	1 - 195	675	Lys-7 to Gln-13.	H0586: 2 and H0494: 1.		
HWHGB32	698891	187	18 - 413	676		H0586: 2 and L0766: 1.		
HWHGB44	716369	188	194 - 415	677		H0586: 2		
HWHGL42	908227	189	1 - 339	678	Pro-10 to Pro-24, Leu-53 to Thr-59, Thr-70 to Lys-81, Met-88 to Thr-93, Glu-101 to Cys-107.	H0592: 1 and H0586: 1.		
HWHGW34	670622	190	2 - 436	679	Ser-11 to Gly-22, Asn-26 to Thr-38, Ser-48 to Gly-54.	H0586: 1 and H0587: 1.		
HWHHA18	665788	191	278 - 451	680	Ser-20 to Gly-29.	H0586: 2		
HWHID04	926251	192	1 - 246	681		H0586: 2, L0777: 2, H0081: 1 and L0747: 1.		
HWHJA12	969044	193	35 - 313	682	Glu-4 to Gly-29, Leu-42 to Trp-51, Ser-71 to Asn-83.	H0586: 2, S0348: 1, H0587: 1, L0809: 1 and L0777: 1.		
HWHPF38	709502	194	2 - 130	683	Asn-23 to Ile-33.	H0587: 2, L0471: 1		

HWHPF60	675703	195	327 - 698	684	Ser-18 to Pro-26.	and L0749: 1. L0748: 2, H0586: 1, H0587: 1, L0749: 1 and L0605: 1.	
HWHPJ63	744720	196	58 - 186	685	Ile-1 to Glu-15.	H0587: 2	
HWHP41	658138	197	96 - 278	686	Gly-11 to Arg-16, Leu-31 to Arg-36.	H0587: 1 and H0540: 1.	
HWHQA86	785281	198	286 - 435	687		H0587: 2	
HWHQI82	739230	199	1 - 216	688	Ser-7 to Gln-16, His-35 to Thr-49.	H0587: 1 and H0494: 1.	
HWHQO07	952660	200	310 - 104	689		H0587: 2	
HWHQO33	670190	201	30 - 335	690	Ser-28 to Arg-34, Thr-53 to Pro-60.	H0586: 2, H0587: 1 and L0777: 1.	
HWHQP22	674151	202	3 - 218	691	Pro-29 to Gln-35.	H0587: 2 and L0794: 1.	
HWHQV08	958709	203	3 - 266	692	Pro-12 to Trp-20.	H0587: 2	
HWHQV13	656647	204	2 - 241	693		H0587: 2	
HWHQV57	734455	205	1 - 516	694	Leu-1 to Asn-18, Gln-39 to Gly-44, Asp-62 to Gln-67, Asn-89 to Leu-94.	H0587: 2	
HWHQX34	703785	206	81 - 263	695	Leu-12 to Asn-18.	H0587: 2	
HWHQX77	771865	207	1 - 357	696	Gly-11 to Ser-18, Pro-49 to Arg-58.	H0587: 2	
HWHQY11	966498	208	559 - 344	697	Arg-1 to Leu-6, Lys-15 to Asn-25.	H0587: 2	
HWHQY18	628987	209	2 - 469	698	Ser-30 to Gly-36.	H0587: 3	
HWHQY36	708384	210	2 - 187	699	Asp-13 to Ser-20.	H0587: 2, L0021: 1, L0747: 1, L0777: 1 and	

HWHRA44	716334	211	3 - 209	700	Phe-1 to Ala-7.	L0755: 1. H0587: 2 and L0655: 1.		
HWHRA91	789529	212	194 - 373	701		H0587: 2	11q23	107680, 107680, 107680, 107680, 107680, 107720, 133780, 147791, 159555, 168000, 186740, 186830, 188025, 203750, 261640, 600048, 601382, 602574, 602574
HWJAC59	761620	213	32 - 109	702	Ala-5 to Lys-25.	H0602: 2		
HWJAC71	760084	214	49 - 228	703	Ser-11 to Arg-20.	H0602: 2		
HWJAD16	661520	215	150 - 311	704	Pro-39 to Gln-44.	L0005: 2, H0602: 1, L0809: 1, L0745: 1, L0758: 1, L0759: 1 and L0592: 1.		
HWHQW24	907997	216	69 - 395	705	Gln-12 to Glu-18, Pro-40 to Gly-47.	L0741: 4 and H0587: 1.		

							Gly-73 to Arg-78, Lys-91 to Gln-100.				
HWHQS58	869780	217	529 - 762	706						H0587: 1 and L0731: 1.	
HWHQQ73	761719	218	34 - 258	707			Lys-1 to Val-10, Arg-59 to Gly-64.			L0748: 3 and H0587: 1.	
HWHQO89	786155	219	162 - 1	708						L0754: 2, H0587: 1 and L0757: 1.	
HWHQL42	805897	220	2 - 226	709			Leu-1 to His-6, Lys-9 to Gly-16, Asn-67 to His-73.			H0587: 1, L0662: 1 and L0666: 1.	
HWHQL26	694021	221	2 - 346	710						H0587: 1 and L0731: 1.	
HWHQJ31	697599	222	304 - 468	711						L0439: 3, H0587: 1, L0805: 1 and L0776: 1.	
HWHQI16	661553	223	61 - 240	712						H0587: 1, L0471: 1 and L0754: 1.	
HWHQH35	707826	224	106 - 336	713			Ser-4 to Arg-22, Pro-24 to Gly-32, His-40 to Ala-45.			L0749: 3, L0748: 2, H0587: 1, L0770: 1 and L0769: 1.	
HWHQB79	774685	225	210 - 569	714						L0748: 2 and H0587: 1.	
HWHPY78	781689	226	396 - 662	715			Glu-1 to Leu-6, Leu-22 to Asn-47, Leu-74 to Gly-80.			L0748: 3 and H0587: 1.	
HWHPR89	598535	227	1 - 252	716						L0747: 2 and H0587: 1.	
HWHPO68	752782	228	117 - 497	717			Thr-7 to Gln-13, Asn-30 to Glu-42,			L0758: 2, H0587: 1 and L0601: 1.	

							Pro-74 to Arg-82, Ser-112 to Thr-124.				
HWHPM27	682719	229	217 - 372	718						L0748: 3, H0587: 1 and L0766: 1.	
HWHPL01	915610	230	295 - 501	719			Gly-59 to Tyr-64.			L0747: 2 and H0587: 1.	
HWHPK76	769791	231	2 - 100	720			Met-13 to Arg-18.			H0587: 1 and L0745: 1.	
HWHPK51	725456	232	141 - 332	721						L0616: 1 and H0587: 1.	
HWHPJ26	681217	233	111 - 320	722			Met-1 to Arg-6, Arg-14 to Arg-26, Thr-35 to Trp-40, Arg-57 to Gly-68.			H0587: 1 and L0740: 1.	
HWHPF78	773407	234	411 - 611	723						L0748: 2 and H0587: 1.	
HWHPD16	661660	235	37 - 738	724			Gln-1 to Lys-17, Pro-19 to Pro-29.			L0740: 3, L0779: 2 and H0587: 1.	
HWHPK04	614960	236	37 - 312	725			Leu-9 to Gly-15, Leu-42 to Cys-56, Ser-66 to Lys-83.			H0587: 1 and L0749: 1.	
HWHPA61	741642	237	125 - 274	726			Cys-23 to Gly-30.			H0587: 1 and L0740: 1.	
HWHKJ11	965201	238	13 - 165	727			Lys-1 to Lys-8, Thr-27 to Ser-35.			H0586: 1 and L0519: 1.	
HWHKG03	971735	239	2 - 880	728			Ser-10 to Gly-15.			H0586: 1, L0766: 1, L0774: 1, L0775: 1 and L0659: 1.	
HWHJM08	955683	240	206 - 427	729			Gly-63 to His-74.			L0754: 5, L0776: 2,	

									L0439: 2, L0745: 2, H0586: 1, L0438: 1, L0750: 1 and L0752: 1.			
HWHJJ11	965189	241	384 - 181	730		Ser-11 to Trp-17, Glu-57 to Ala-68.			L0759: 2, H0586: 1 and L0638: 1.			
HWHHW50	724078	242	3 - 170	731		Thr-32 to Pro-37.			H0586: 1 and L0777: 1.			
HWHHU57	734458	243	187 - 372	732					H0586: 1, L0756: 1 and L0777: 1.			
HWHHQ10	963959	244	77 - 316	733		Thr-17 to Gly-24, Lys-74 to Lys-80.			H0586: 1 and L0527: 1.			
HWHHO76	769848	245	272 - 529	734					L0756: 2 and H0586: 1.			
HWHHL02	919202	246	234 - 428	735		Phe-10 to Lys-15.			H0586: 1 and L0777: 1.			
HWHGX86	970662	247	553 - 810	736		Asn-1 to Gly-11, Arg-22 to Arg-28, Gly-32 to Ser-52, Phe-56 to Ile-64, Gly-68 to Gln-76.			H0586: 1, L0455: 1 and L0589: 1.			
HWHGY82	779020	248	232 - 420	737					H0586: 1 and L0748: 1.			
HWHGY56	733124	249	32 - 409	738					L0439: 2 and H0586: 1.	22q13.33		
HWHGW72	945692	250	100 - 939	739					AR054: 23, AR050: 16, AR051: 3, AR089: 1, AR061: 1 H0586: 1 and L0375: 1.			

947361	496	327 - 1	985	Gly-1 to Gly-7, Ala-13 to Gln-21, Ala-43 to Ser-48, Asn-67 to Gly-75, Pro-82 to Pro-90.			
HWHGS51	725446	251	740	Gly-22 to Met-29.	H0586: 1, L0766: 1 and L0439: 1.		
HWHGP95	795148	252	741		L0748: 4 and H0586: 1.		
HWHGF95	947019	253	742	Glu-25 to Trp-33, Trp-76 to Gln-83, Pro-94 to Asp-108.	AR050: 3, AR061: 2, AR054: 2, AR089: 1, AR051: 0 H0586: 1 and L0376: 1.		
HWHGE01	915933	254	743	His-10 to Ser-16, Lys-35 to Asn-43, Ile-56 to Ala-72.	H0586: 1, L0748: 1 and L0752: 1.		
HWHGC93	915311	255	744		H0586: 1 and L0744: 1.		
HWHGC57	942388	256	745	Arg-10 to Asp-22.	AR089: 8, AR061: 4 H0586: 1		
HWHGB85	889955	257	746		H0586: 1 and L0764: 1.	11ql3	102200, 106100, 131100, 131100, 131100, 131100, 133780, 147050, 153700, 161015,

									164009, 168461, 168461, 168461, 180721, 180840, 191181, 193235, 209901, 232600, 259700, 259770, 600045, 600319, 600528, 601884	
HWHGB13	656712	258				350 - 544	747		H0586: 1	
HWFBH55	732549	259				471 - 274	748		T0004: 1 and L0766: 1.	
HWFBG80	561208	260				119 - 394	749	Gly-13 to Pro-19, Arg-25 to Pro-31, Thr-43 to Gln-48.	AR050: 111, AR051: 106, AR054: 94 T0004: 1	
HWFBD96	796070	261				47 - 271	750		T0004: 1	
HWFBH09	575533	262				162 - 320	751		T0004: 1	
HWFAD94	504477	263				493 - 344	752	Pro-14 to Tyr-19.	T0004: 1	
HWFAD84	504489	264				620 - 372	753		T0004: 1	
HWFAD65	753943	265				261 - 404	754		T0004: 1 and L0758: 1.	
HWEAE94	794026	266				59 - 418	755		H0601: 1 and L0601: 1.	
HWEAD10	927208	267				260 - 108	756		H0601: 1, L0770: 1, L0772: 1 and L0775: 1.	

HWDAY07	952441	268	246 - 995	757	Asn-8 to Lys-13, Leu-52 to Arg-59, Glu-156 to Trp-161, Pro-200 to Asp-207.	H0600: 1, L0740: 1 and L0777: 1.		
HWDA521	670233	269	54 - 236	758	Tyr-52 to Glu-57.	H0600: 1 and L0757: 1.		
HWDA89	795713	270	2 - 208	759	Val-1 to Thr-6.	L0747: 2 and H0600: 1.		
HWDA090	788546	271	1 - 246	760		H0600: 1 and L0748: 1.		
HWDA063	744591	272	1 - 333	761		L0748: 2 and H0600: 1.		
HWDA132	698628	273	136 - 327	762	Tyr-6 to His-14.	L0743: 2, H0600: 1, L0637: 1, L0653: 1, L0776: 1, L0744: 1, L0747: 1, L0780: 1 and L0757: 1.		
HWDAK75	973099	274	214 - 348	763	Lys-1 to Thr-12, His-37 to Lys-45.	H0600: 1		
HWDA72	766077	275	143 - 280	764	Pro-35 to Phe-40.	H0600: 1 and L0749: 1.		
HWDA54	729262	276	283 - 432	765		H0600: 1 and L0748: 1.		
HWDA40	881233	277	172 - 426	766	Gln-12 to Arg-21, Arg-35 to Gln-40.	H0600: 1 and L0783: 1.		
HWDA55	731414	278	258 - 404	767		H0600: 1 and L0439: 1.		
HSTAO59	908993	279	1 - 357	768	Ile-28 to Lys-36, Thr-58 to Cys-65,	AR089: 0, AR061: 0 H0068: 1, L0759: 1		

							His-85 to Lys-92, Tyr-98 to Ser-104, Ser-112 to Gly-117.	and L0595: 1.		
HSTAH84	783227	280	3 - 308	769			Ala-40 to His-46.	H0068: 1		
HSTAG60	578487	281	41 - 277	770			Asp-3 to Arg-17, Cys-55 to Tyr-63.	H0068: 1		
HOUIF71	759929	282	156 - 407	771			Arg-13 to Arg-22.	L0748: 2 and S0342: 1.		
HOUIGC71	760110	283	1 - 171	772				S0040: 1 and L0748: 1.		
HOUFM73	764173	284	3 - 197	773				S0040: 1 and L0745: 1.		
HOUFM67	751325	285	37 - 126	774			Ser-4 to Asp-11.	S0040: 1		
HOUFM50	724038	286	124 - 267	775			Ser-27 to Ala-34, Tyr-42 to Asn-48.	S0040: 1 and L0471: 1.		
HOUFM32	698816	287	161 - 301	776				S0040: 1		
HOUFD93	791584	288	134 - 274	777			Met-1 to Gln-14.	L0589: 2 and S0040: 1.		
HOUFD09	625245	289	1 - 303	778				S0040: 1 and L0757: 1.		
HOUFC52	726438	290	71 - 178	779				S0040: 1 and L0756: 1.	lp32-p34	120950, 120960, 130500, 133200, 138140, 168360, 171760, 171760, 176100, 176100, 178300, 187040, 230000, 255800,

										600101, 600650, 600650, 600722, 600722
HOUET93	792495	291	2 - 250	780				S0040: 1 and L0749: 1.		
HOUES18	577112	292	190 - 393	781				L0749: 3, L0748: 2, S0040: 1 and L0768: 1.		
HOUER77	772417	293	52 - 222	782				S0040: 1 and L0594: 1.		
HOUEM24	677416	294	1 - 165	783				S0040: 1 and L0766: 1.		
HOU EK01	965449	295	126 - 344	784	Thr-3 to Phe-11.			L0748: 2, S0040: 1, L0772: 1 and L0757: 1.	15q15	177070, 177070, 182500, 218000, 227220, 243500, 600839, 601800
HOU EH51	725820	296	160 - 324	785				L0740: 2 and S0040: 1.		
HOU EG85	883933	297	2 - 388	786	Gln-43 to Asp-54, Arg-99 to Arg-108.			L0777: 2 and S0040: 1.		
HOU DR29	576473	298	42 - 170	787	Gly-32 to Gln-38.			S0040: 1		
HOU DL40	710868	299	381 - 253	788	Arg-1 to Asp-6.			S0040: 1		
	858895	497	249 - 148	986						
HOU CZ30	573930	300	141 - 308	789				S0040: 1		
HOU CR25	559993	301	41 - 244	790				S0040: 1 and L0752: 1.		
HOU BO69	757808	302	19 - 162	791	Lys-39 to Lys-46.			S0040: 1 and L0731: 1.		
HOU BD18	858911	303	100 - 387	792				S0040: 1 and L0366: 1.		
HOU BB11	965041	304	3 - 368	793	Pro-6 to Ser-13.			L0766: 2 and S0040: 1.		

[illegible]

HKAHP85	783955	318	38 - 337	807	Pro-68 to Ser-75.	H0494: 1 and L0749: 1.		
HKAHI69	916528	319	254 - 637	808	Asn-1 to Leu-6, Pro-28 to Asn-33.	H0494: 1, L0748: 1, L0740: 1 and L0747: 1.		
HKAHE93	791860	320	23 - 247	809	Asp-4 to Asn-11, Asn-46 to Thr-56.	L0439: 4 and H0494: 1.		
HKAHA10	857339	321	1 - 291	810	Ser-23 to Arg-28, Met-38 to Lys-45, Val-63 to Gly-73.	H0494: 1 and L0592: 1.	1p36.2	120550, 120570, 120575, 130500, 133200, 153454, 167410, 256700, 600975
HKAGC23	912677	322	237 - 434	811	Pro-27 to Gly-33.	H0494: 1, L0744: 1 and L0748: 1.		
HKAFR01	916400	323	260 - 400	812	Phe-20 to Asn-25.	L0766: 3, H0494: 1 and L0638: 1.		
HKAFAQ61	741786	324	404 - 622	813		H0494: 1, L0748: 1 and L0439: 1.		
HKA FN96	796361	325	68 - 319	814	Ser-20 to Gly-25.	H0494: 1 and L0744: 1.		
HKA FD03	924048	326	148 - 345	815	Ala-20 to Lys-32.	H0494: 1 and L0766: 1.		
HKA EJ79	917408	327	1 - 171	816	Gly-52 to Pro-57.	H0494: 1 and L0439: 1.		
HKA EG61	925951	328	400 - 2	817		H0494: 1, L0773: 1 and L0803: 1.		

HKADR84	800106	329	53 - 328	818	Pro-20 to Trp-29, Thr-38 to Ala-45.	AR050: 60, AR054: 46, AR051: 44 H0494: 1		
HKADP50	971356	330	3 - 833	819	Pro-18 to Ala-28, Arg-33 to Trp-48, His-50 to Pro-57, Pro-64 to Gly-78, Gly-126 to Phe-140, Ser-144 to Lys-149, Phe-172 to Tyr-178.	AR054: 186, AR050: 156, AR051: 140, AR089: 62, AR061: 28 H0494: 1 and L0803: 1.		
HKADP11	966941	331	3 - 416	820	Pro-17 to Arg-22, Ala-83 to Gly-88, Leu-109 to Gln-114.	L0803: 2 and H0494: 1.		
HKADO84	911567	332	1 - 261	821	Asp-27 to Cys-37, Ser-49 to Gln-54.	L0809: 3, H0494: 1, L0363: 1, L0789: 1 and L0601: 1.		
HKADG12	638194	333	44 - 220	822	Arg-6 to Ser-13, Gln-30 to Gln-36.	H0494: 1 and L0766: 1.		
	968887	498	427 - 191	987	Pro-20 to Trp-31, Tyr-66 to Arg-76.			
HKACX88	970793	334	179 - 3	823	Tyr-15 to Val-35, Pro-38 to Asp-44, Arg-52 to Lys-59.	H0494: 1		
HKACX62	744273	335	265 - 672	824	Asp-10 to Ser-22.	H0494: 1 and L0741: 1.		
HKACX25	678045	336	73 - 288	825	His-15 to Glu-21.	H0494: 1 and L0749: 1.		
HKACU02	919850	337	149 - 376	826	Ser-17 to Pro-23, Thr-42 to His-53.	H0494: 1, L0602: 1 and L0748: 1.		
HKACP26	422255	338	33 - 188	827		H0494: 1 and L0596:		

HKACP23	881718	339	2 - 442	828	Gly-1 to Ala-6, Pro-21 to Gly-27, Ser-43 to Gly-51, Ser-77 to Ser-105.	1. H0494: 1			
HKACO69	614156	340	1 - 315	829	Pro-1 to Leu-14, Pro-16 to Ser-22, Ser-28 to His-33, Ser-65 to Gly-77, Pro-79 to Ala-90.	H0494: 1			
HKACO22	674494	341	499 - 636	830	Asn-1 to Asp-10.	H0494: 1 and L0748: 1.			
HKACL83	881711	342	1 - 573	831		H0494: 1, L0800: 1 and L0439: 1.			
HKACK91	789430	343	163 - 345	832	Trp-2 to Gln-16.	H0494: 1 and L0741: 1.			
HKACI41	924045	344	2 - 391	833	Ser-16 to Arg-41.	H0494: 1 and L0601: 1.	3		
HKABY40	650852	345	239 - 463	834	Arg-13 to Ile-21, Pro-42 to Thr-54.	H0494: 1, L0438: 1 and L0439: 1.			
HKABW75	973331	346	3 - 74	835		H0494: 1			
HKABU90	788888	347	3 - 422	836	Ala-10 to Ser-15.	H0494: 1, L0740: 1 and L0593: 1.			
HKABR92	879400	348	53 - 313	837		H0494: 1 and L0747: 1.			
HKABQ76	857381	349	166 - 513	838	Arg-10 to Leu-15, Gln-31 to Trp-36, Glu-44 to Glu-59.	L0750: 2 and H0494: 1.			
HKABM34	703452	350	3 - 257	839		H0494: 1 and L0589:			

HKABE53	892078	351	1 - 318	840	Lys-27 to Tyr-33, Ser-65 to Pro-71, Gly-99 to Trp-106.	1. H0494: 1, L0776: 1 and L0751: 1.		
HKAAD24	787545	352	70 - 336	841	Ser-6 to Arg-14, Val-36 to Gly-42.	H0494: 1 and L0439: 1.		
HFEBY03	973292	353	171 - 329	842	Lys-6 to Gly-11, Trp-19 to Arg-26, Met-38 to Gly-53.	H0081: 1		
HFEBQ59	739355	354	2 - 295	843	Arg-14 to Trp-23.	H0081: 1 and L0759: 1.		
HFEBP01	916728	355	1 - 330	844	Arg-14 to His-23, Pro-26 to Lys-37.	H0081: 1, L0471: 1 and L0438: 1.		
HFEBJ61	576092	356	1 - 177	845	Thr-20 to Gln-25.	H0081: 1		
HFEBH07	953523	357	109 - 279	846	Glu-12 to Pro-19.	L0599: 2 and H0081: 1.		
HFEBD01	916725	358	42 - 191	847	Val-18 to Tyr-25.	H0081: 1 and L0532: 1.		
HFEBA06	935685	359	26 - 217	848	Gly-53 to Lys-59.	L0539: 1 and H0081: 1.		
HFEAU06	960609	360	72 - 386	849	Ser-18 to Gly-26, Glu-39 to Glu-51.	H0081: 1, L0754: 1 and L0755: 1.		
HFEAN03	925408	361	3 - 149	850		H0081: 1 and L0366: 1.		
HFEAJ78	855319	362	3 - 176	851		AR054: 9, AR051: 2, AR050: 2 H0081: 1		
HFEAI72	700631	363	253 - 447	852	Glu-52 to Ser-62.	H0081: 1 and L0742: 1.		

HFEAI49	722129	364	2 - 178	853	Lys-43 to Thr-52.	L0757: 4, H0081: 1 and L0747: 1.		
HFEAH01	916068	365	261 - 40	854	Asp-8 to Tyr-17.	H0081: 1 and L0749: 1.		
HFEAG41	504596	366	187 - 423	855	Gly-16 to Ala-26, Ser-40 to Ser-46, Cys-54 to Ala-61.	L0747: 3 and H0081: 1.		
HESAC55	518730	367	2 - 67	856		H0086: 1		
HESAC45	537453	368	15 - 173	857		H0086: 1		
HERAS77	772471	369	5 - 139	858		H0345: 1		
HERAS69	974532	370	119 - 379	859		H0345: 1		
HERAN59	739562	371	2 - 112	860		L0748: 3 and H0345: 1.	3q26.2-qter	
HERAN52	855536	372	47 - 166	861	Pro-1 to Glu-18, Gly-34 to Asp-40.	L0748: 2 and H0345: 1.		
HERAN24	855537	373	215 - 376	862	Arg-8 to Lys-14, Ser-33 to Arg-45.	H0345: 1 and L0748: 1.		
HERAN16	973714	374	9 - 173	863	Pro-1 to Gly-9, Gly-32 to Gln-40.	H0345: 1		
HERAN06	954671	375	106 - 321	864	Phe-54 to Glu-59.	L0365: 1 and H0345: 1.		
HERAL72	529196	376	157 - 291	865	Ser-17 to Ser-25.	AR051: 20, AR054: 17, AR050: 10 H0345: 1		
HERAK96	796591	377	3 - 131	866		H0345: 1 and L0600: 1.		
HERAK20	855546	378	22 - 273	867		H0345: 1		
HERAK01	921634	379	1 - 135	868	Pro-5 to Asn-13, Cys-23 to Lys-28,	L0520: 1 and H0345: 1.		

HERAH85	928415	380	2 - 367	869	Gln-36 to Cys-42.	AR051: 49, AR050: 40, AR054: 33 H0345: 1		
HERAH37	707573	381	330 - 635	870		H0345: 1 and L0439: 1.		
HERAH16	880475	382	12 - 158	871	Arg-37 to Arg-47.	L0794: 1 and H0345: 1.		
HERAH06	954672	383	471 - 644	872	Lys-14 to Asp-31.	L0766: 5, L0803: 2, L0779: 2, H0345: 1, L0777: 1 and L0758: 1.		
HERAG53	728441	384	105 - 332	873	Thr-1 to Glu-8, Pro-10 to Ala-16, Leu-25 to Asn-31.	H0345: 1 and L0748: 1.		
HERAE59	739569	385	53 - 169	874		H0345: 1 and L0745: 1.		
HERAE24	678518	386	298 - 480	875	Glu-1 to Pro-22, Lys-46 to Lys-54.	H0345: 1 and L0603: 1.		
HERAD94	793020	387	11 - 295	876	Ala-33 to Ser-39, Ala-49 to Gln-63.	H0345: 1 and L0755: 1.		
HERAD26	520370	388	499 - 308	877		AR054: 274, AR051: 97, AR050: 91 H0345: 1		
HERAC89	787123	389	250 - 408	878		H0345: 1 and L0748: 1.		
HERAB53	727373	390	177 - 410	879		H0345: 1 and L0743: 1.		
HBIPD10	961972	391	3 - 140	880		H0593: 1 and L0748: 1.		

HBIPB07	951981	392	1 - 228	881	Glu-66 to Val-73.	H0593: 1 and L0756: 1.		
HBIOZ10	973131	393	3 - 503	882	Leu-50 to Asp-61, Ser-100 to Leu-107, Ala-120 to Thr-130.	AR054: 189, AR051: 68, AR050: 35, AR089: 4, AR061: 3, H0593: 1		
HB1OW11	965551	394	3 - 377	883	Asn-2 to Ser-17, Gly-28 to Gly-33, Arg-39 to Cys-45.	L0731: 2 and H0593: 1.		
HB1OT01	914657	395	428 - 691	884	Arg-1 to Arg-9.	L0518: 2, H0593: 1 and L0748: 1.		
HB1OM94	973137	396	449 - 760	885	Trp-1 to Asp-13.	AR089: 10, AR061: 4, L0759: 2 and H0593: 1.		
HB1OJ47	973132	397	140 - 520	886	Asp-1 to Thr-13, Pro-24 to Arg-39, Ser-50 to Ser-64.	H0593: 1		
HB1OJ05	930754	398	1 - 240	887	Arg-9 to Arg-16.	L0369: 1, H0593: 1 and L0749: 1.		
HB1OF05	930771	399	412 - 618	888	Pro-2 to Pro-9, Leu-18 to Ser-27, Pro-58 to Thr-69.	L0748: 2, L0581: 2, L0774: 1, H0593: 1 and L0752: 1.		
HB1MT11	965089	400	456 - 674	889		L0060: 1, H0593: 1 and L0759: 1.	4p16.3	134934, 134934, 134934, 134934, 134934, 143100, 180072, 180072,

									194190, 252800, 252800, 252800, 600965
HBIMR08	957996	401	462 - 148	890	Lys-7 to Thr-19, Pro-27 to Ser-32.	H0593: 1, L0749: 1 and L0777: 1.			
HBFA23	504560	402	75 - 206	891	Thr-39 to Lys-44.	T0001: 1			
HAWCB26	685045	403	310 - 540	892		T0060: 1, L0749: 1 and L0731: 1.			
HAWAZ32	702976	404	69 - 194	893	Ser-11 to Pro-24, Arg-29 to Ile-42.	T0060: 1, L0803: 1 and L0594: 1.			
HAWAY15	829255	405	55 - 375	894		L0748: 2 and T0060: 1.			
HAWAW12	971497	406	53 - 190	895	Lys-1 to Asn-7, Ser-38 to Arg-46.	T0060: 1 and L0596: 1.			
HAWAS28	416137	407	44 - 241	896		T0060: 1 and L0756: 1. Xq12			300011, 300011, 300011, 300127, 305450, 313700, 313700, 313700, 313700, 313700
HAWAQ06	960762	408	403 - 654	897	Pro-26 to Asp-36.	T0060: 1, L0545: 1 and L0748: 1.			
HAWAA53	864417	409	195 - 428	898		T0060: 1 and L0756: 1.			
HAVAF22	675054	410	74 - 250	899	Tyr-3 to Cys-9.	H0344: 1 and L0581: 1.			

HAVAC03	925291	411	97 - 444	900			L0749: 5 and H0344: 1.		
HARNO54	729117	412	36 - 305	901			H0592: 1 and L0439: 1.		
HARNI55	731232	413	5 - 202	902			H0592: 1 and L0748: 1.		
HARND69	754675	414	31 - 267	903			H0592: 1, L0747: 1 and L0777: 1.		
HARNB30	731614	415	1 - 411	904	Gln-30 to Gly-36, Pro-41 to His-56.		H0592: 1 and L0748: 1.		
HARMV85	864612	416	313 - 456	905	Lys-1 to Ser-9.		H0592: 1 and L0365: 1.		
HARMP93	791948	417	283 - 462	906	Thr-40 to Ile-46.		H0592: 1 and L0745: 1.		
HARMM53	854369	418	155 - 505	907	Ile-14 to Asp-20, Gly-30 to Gly-35, Lys-44 to Ile-49, Val-56 to Trp-76, Leu-78 to Arg-83, Glu-89 to Arg-94.		L0439: 2 and H0592: 1.		
HARMA51	725137	419	2 - 298	908	Ala-15 to Arg-20, Ser-31 to Gly-36.		H0592: 1 and L0748: 1.		
HADXB70	757287	420	148 - 456	909			H0443: 1 and L0748: 1.		
HADGI45	717755	421	288 - 452	910	Gln-8 to Ser-17, Cys-20 to Asp-25, Arg-39 to Val-46, Leu-50 to Arg-55.		L0803: 2, L0809: 2, L0748: 2, L0749: 2, L0731: 2, L0781: 1, H0427: 1, L0804: 1, L0659: 1, L0789: 1 and L0663: 1.		

HADGG22	674421	422	200 - 484	911	Lys-45 to Glu-50, Ile-56 to Arg-63.	L0748: 4, L0754: 2, L0717: 1, H0427: 1, L0638: 1, L0521: 1, L0783: 1, L0809: 1 and L0792: 1.		
HADGC96	865247	423	54 - 185	912		H0427: 1 and L0748: 1.		
HADGB52	647367	424	191 - 325	913	Glu-1 to Phe-6.	H0427: 1 and L0747: 1.		
HADGB01	916374	425	223 - 393	914	Gly-1 to Cys-6, Pro-27 to Lys-37.	H0427: 1 and L0748: 1.		
HADFZ81	420937	426	78 - 278	915	Gly-2 to Asp-10.	H0427: 1, L0746: 1 and L0592: 1.		
HADFZ14	848980	427	178 - 528	916	His-33 to Arg-38, Lys-105 to Lys-113.	H0427: 1 and L0749: 1.		
HADFW15	848983	428	290 - 565	917	Gln-36 to Glu-49, Pro-78 to Gly-83.	L0562: 1 and H0427: 1.		
HADFW06	935340	429	33 - 302	918	Asp-1 to His-6, Leu-34 to Cys-39, Ser-44 to Cys-51, Ala-63 to Phe-70.	H0427: 1 and L0604: 1.		
HADFV03	972437	430	1 - 249	919		H0427: 1		
HADFT70	757158	431	156 - 308	920	Arg-8 to Glu-13, Val-25 to Ser-30.	H0427: 1 and L0754: 1.		
HADFJ08	959297	432	83 - 346	921		H0427: 1 and L0438: 1.		
HADFG90	788865	433	225 - 455	922	Leu-5 to Arg-10, Leu-40 to Asn-55.	L0748: 2 and H0427: 1.		
HADFD69	754277	434	1 - 432	923	Lys-6 to Asn-14,	H0427: 1 and L0362:		

HADFC15	659541	435	212 - 322	924	Ala-26 to Gln-40, Asp-44 to Glu-51, Arg-114 to Leu-125, Arg-133 to Gly-138.	1.	L0803: 2, L0756: 2, H0427: 1, L0763: 1, L0439: 1, L0752: 1 and L0759: 1.		
HADFB60	740318	436	79 - 441	925	Pro-104 to Gly-110.	1.	H0427: 1 and L0756:		
HADFB55	731686	437	275 - 487	926		1.	H0427: 1 and L0743:		
HADFB08	959273	438	146 - 289	927			H0427: 1		
HADEY09	625505	439	164 - 280	928		1.	H0427: 1 and L0731:		
HADEU65	747880	440	212 - 415	929	Arg-27 to Thr-39, Lys-51 to Lys-60.	1.	H0427: 1 and L0748:		
HADEU32	699194	441	148 - 291	930			H0427: 1, L0021: 1, L0805: 1 and L0595: 1.		
HADET68	906389	442	596 - 769	931	Arg-25 to Lys-32, Arg-53 to Trp-58.	1.	H0427: 1 and L0591:		
HADDS75	660816	443	463 - 254	932			H0427: 1	17q11-qter	
HADDS21	670802	444	11 - 226	933	Gly-4 to Lys-10, Gln-36 to Glu-41, Arg-61 to Ser-72.		H0427: 1		
HADDS07	849000	445	49 - 291	934	Ser-1 to Gln-9, Val-17 to Gly-25.		H0427: 1		
HADDR20	669609	446	121 - 288	935	Thr-1 to Lys-7, Pro-16 to Ile-25,	1.	H0427: 1 and L0766:		

HADDQ56	733340	447	192 - 344	936	Phe-40 to Ser-49.	L0748: 2 and H0427: 1.		
HADDP12	970537	448	38 - 154	937		H0427: 1		
HADDI89	865278	449	110 - 265	938		H0427: 1		
HADDI54	729760	450	89 - 202	939	Ser-8 to Gly-13.	H0427: 1		
HADDI42	713700	451	115 - 2	940		H0427: 1		
HADDE27	683382	452	3 - 215	941		H0427: 1 and L0754: 1.		
HADDE15	952542	453	2 - 790	942	Asn-1 to Pro-9.	H0427: 1, L0804: 1, L0748: 1 and L0731: 1.		
HADDC94	794266	454	263 - 544	943		H0427: 1 and L0741: 1.		
HADDC64	469113	455	108 - 266	944	Gly-7 to Asn-12, Ser-29 to Asn-34.	H0427: 1		
HADDC44	715928	456	2 - 178	945		H0427: 1		
HADDC42	713657	457	7 - 231	946	Glu-10 to Arg-19, Ser-35 to Asp-44, Ser-61 to Ser-69.	H0427: 1		
HADDC05	932066	458	270 - 488	947	Arg-32 to Lys-38.	H0427: 1		
HADDB62	743476	459	296 - 520	948		H0427: 1		
HADDB13	657120	460	216 - 320	949		H0427: 1		
HADDA04	925627	461	1 - 183	950	Val-3 to Lys-14.	H0427: 1		
HADCZ08	959304	462	70 - 189	951	Ser-10 to Asn-18.	H0427: 1 and L0517: 1.		
HADCX34	704030	463	37 - 306	952		L0756: 2 and H0427: 1.		
HADCW01	916399	464	188 - 361	953		L0751: 2, H0427: 1, L0759: 1 and L0361: 1.		

HADCP73	764391	465	328 - 462	954		H0427: 1		
HADCP50	723684	466	109 - 252	955	Asn-1 to Gly-7, Val-20 to Lys-30, Pro-39 to Val-45.	H0427: 1		
HADCO30	914688	467	2 - 253	956	Gly-10 to Leu-15.	H0427: 1 and L0747: 1.		
HADCO03	924043	468	306 - 506	957		H0427: 1, L0777: 1 and L0731: 1.		
HADCN29	690600	469	105 - 305	958		H0427: 1 and L0777: 1.		
HADCH77	826137	470	215 - 343	959		H0427: 1 and L0748: 1.		
HADCD46	719005	471	284 - 418	960	Cys-17 to Arg-25.	L0731: 4 and H0427: 1.		
HADAY29	690602	472	63 - 203	961	Glu-1 to Glu-8, Ser-26 to Lys-40.	H0427: 1 and L0748: 1.		
HADAS83	490455	473	275 - 3	962	Pro-11 to Cys-16, Pro-75 to Arg-91.	H0427: 1		
	564848	499	233 - 499	988	Ser-19 to Phe-25, Ser-43 to Gly-57.			
HADAR23	675844	474	156 - 395	963	Gly-3 to Pro-9, Ala-40 to His-55, His-63 to Arg-69, Pro-74 to Ser-80.	L0600: 2 and H0427: 1.		
HADAM60	740326	475	288 - 395	964		H0427: 1 and L0599: 1.		
HADAE96	796469	476	2 - 145	965	Gln-10 to Asp-15, Asn-24 to Pro-29.	L0741: 3 and H0427: 1.		
HADAE92	792823	477	195 - 473	966	Thr-1 to Lys-11,	H0427: 1 and L0754:		

HACBW79	774898	478	335 - 454	967	His-30 to Trp-37.	1.	L0756: 2, S0280: 1, L0740: 1 and L0759: 1.		
HACCT11	966886	479	168 - 332	968	Arg-9 to Tyr-14.		S0280: 1 and L0521: 1.		
HACBW76	849054	480	36 - 224	969	Glu-16 to Val-21, Thr-36 to Leu-47.		L0005: 1, S0280: 1 and L0764: 1.		
HACBU26	683006	481	134 - 412	970	Val-49 to Lys-60.		S0280: 1 and L0748: 1.		
HACBO10	964459	482	403 - 609	971	Ser-8 to Ser-19, Lys-37 to Trp-49, Tyr-53 to Val-58.		L0717: 2, L0775: 2, S0280: 1 and L0806: 1.		
HACBN71	872015	483	30 - 470	972			S0280: 1 and L0740: 1.		
HACBJ83	875263	484	3 - 473	973	Pro-17 to Ala-23, Gly-33 to Pro-39, Gln-49 to Pro-59, Gly-98 to Gln-106.		S0280: 1, L0743: 1 and L0746: 1.		
HACBJ17	663371	485	3 - 341	974	Ile-5 to Ser-18, Gly-35 to Tyr-44, His-69 to Gly-75.		L0439: 3 and S0280: 1.		
HACBH42	933951	486	72 - 497	975	Val-33 to Pro-49, Pro-52 to Arg-58, Thr-91 to Gly-101.		S0280: 1 and L0777: 1.		
HACBB13	698800	487	312 - 49	976	Ile-56 to Asp-62.		S0280: 1 and L0748: 1.		
HACAB93	792382	488	2 - 229	977	Cys-1 to Gln-14.		S6022: 1 and L0766: 1.		
HACAA57	733887	489	137 - 364	978	Arg-17 to Ile-22.		S6022: 1, L0745: 1 and L0746: 1.		
HACAA03	924513	490	33 - 374	979			S6022: 1 and L0764: 1.		
HABGA24	676827	491	2 - 199	980			L0766: 5, L0803: 4, L0756: 2, S0348: 1, L0717: 1, L0021: 1,		

					L0483: 1, L0774: 1, L0750: 1, L0759: 1 and L0589: 1.		
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Table 1A. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly.

[052] Column 7 in Table 1A provides an expression profile and library code; count for each of the contig sequences (SEQ ID NO:X) disclosed in Table 1A, which can routinely be combined with the information provided in Table 4 and used to determine the normal or diseased tissues, cells, and/or cell line libraries which predominantly express the polynucleotides of the invention. The first number in column 7 (preceding the colon), represents the tissue/cell source identifier code corresponding to the code and description provided in Table 4. For those identifier codes in which the first two letters are not "AR", the second number in column 7 (following the colon) represents the number of times a sequence corresponding to the reference polynucleotide sequence was identified in the tissue/cell source. Those tissue/cell source identifier codes in which the first two letters are "AR" designate information generated using DNA array technology. Utilizing this technology, cDNAs were amplified by PCR and then transferred, in duplicate, onto the array. Gene expression was assayed through hybridization of first strand cDNA probes to the DNA array. cDNA probes were generated from total RNA extracted from a variety of different tissues and cell lines. Probe synthesis was performed in the presence of ³³P dCTP, using oligo(dT) to prime reverse transcription. After hybridization, high stringency washing conditions were employed to remove non-specific hybrids from the array. The remaining signal, emanating from each gene target, was measured using a Phosphorimager. Gene expression was reported as Phosphor Stimulating Luminescence (PSL) which reflects the level of phosphor signal generated from the probe hybridized to each of the gene targets represented on the array. A local background signal subtraction was performed before the total signal generated from each array was used to normalize gene expression between the different hybridizations. The value presented after "[array code]:" represents the mean of the duplicate values, following background subtraction and probe normalization. One of skill in the art could routinely use this information to identify normal and/or diseased tissue(s) which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue and/or cell expression. The sequences disclosed herein have been determined to be predominantly expressed in connective tissues, including normal and diseased connective tissues (See Table 1A, column 7 and Table 4).

[053] Column 8 in Table 1A provides a chromosomal map location for certain polynucleotides of the invention. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Each sequence in the UniGene database is assigned to a "cluster"; all of the ESTs, cDNAs, and STSs in a cluster are believed to be derived from a single gene. Chromosomal mapping data is often available for one or more sequence(s) in a UniGene cluster; this data (if consistent) is then applied to the cluster as a whole. Thus, it is possible to infer the chromosomal location of a new polynucleotide sequence by determining its identity with a mapped UniGene cluster.

[054] A modified version of the computer program BLASTN (Altshul et al., J. Mol. Biol. 215:403-410 (1990), and Gish et al., Nat. Genet. 3:266-272 (1993)) was used to search the UniGene database for EST or cDNA sequences that contain exact or near-exact matches to a polynucleotide sequence of the invention (the 'Query'). A sequence from the UniGene database (the 'Subject') was said to be an exact match if it contained a segment of 50 nucleotides in length such that 48 of those nucleotides were in the same order as found in the Query sequence. If all of the matches that met this criteria were in the same UniGene cluster, and mapping data was available for this cluster, it is indicated in Table 1A under the heading "Cytologic Band". Where a cluster had been further localized to a distinct cytologic band, that band is disclosed; where no banding information was available, but the gene had been localized to a single chromosome, the chromosome is disclosed.

[055] Once a presumptive chromosomal location was determined for a polynucleotide of the invention, an associated disease locus was identified by comparison with a database of diseases which have been experimentally associated with genetic loci. The database used was the Morbid Map, derived from OMIM™ (*supra*). If the putative chromosomal location of a polynucleotide of the invention (Query sequence) was associated with a disease in the Morbid Map database, an OMIM reference identification number was noted in column 9, Table 1A, labeled "OMIM Disease Reference(s)". Table 5 is a key to the OMIM reference identification numbers (column 1), and provides a description of the associated disease in Column 2.

TABLE 1B

Clone ID NO:Z	SEQ ID NO:X	CONTIG ID:	BAC ID: A	SEQ ID NO:B	EXON From-To
HACBA49	14	722875	AC078913	989	1-436
HACBA49	14	722875	AC078913	990	1-263
HACBT81	15	855720	AL136332	991	1-116 244-618 1399-1481 2637-2724 2842-2957 3010-3244 3302-3740 3879-4367 4407-4484 4783-5307 5981-6056 6472-6806 6903-7024 7110-7225 7843-8458 8924-9255 10786-10887 12006-12616 13979-15061
HACBT81	15	855720	AL136332	992	1-140
HACCY20	16	845144	AC069276	993	1-117 548-624 1839-1865
HADAM69	18	699190	AC048337	994	1-464
HADAM69	18	699190	AC073650	995	1-1925 2429-3003 3615-4033 4226-4431 4670-4764 4797-6504 6808-7502 7742-8205 8627-8847
HADAM69	18	699190	AC048337	996	1-695
HADAM69	18	699190	AC073650	997	1-191
HADCO14	22	657572	AC012351	998	1-308
HADCO14	22	657572	AC004933	999	1-308
HADCO14	22	657572	AC073462	1000	1-308
HADCO14	22	657572	AC006028	1001	1-308
HADCO14	22	657572	AC012351	1002	1-277
HADCO14	22	657572	AC012351	1003	1-266

HADCO14	22	657572	AC004933	1004	1-299
HADCO14	22	657572	AC006028	1005	1-239
HADCO14	22	657572	AC006028	1006	1-266
HADCO44	23	716559	AC021078	1007	1-356
HADCO44	23	716559	AC021078	1008	1-794
HADCO48	24	865306	AP002790	1009	1-312
HADCO48	24	865306	AC064801	1010	1-312
HADCO48	24	865306	AP002790	1011	1-603
HADCO48	24	865306	AC064801	1012	1-603
HADCO57	26	734705	AC074077	1013	1-349
HADCX38	30	705751	AL353578	1014	1-438
HADCX38	30	705751	AL133477	1015	1-438
HADCX38	30	705751	AL353578	1016	1-341
HADCX38	30	705751	AL133477	1017	1-208
HADCX38	30	705751	AL133477	1018	1-341
HADDB75	31	757028	AC068936	1019	1-86 397-508 4158-4277 4607-4781 4820-5422 5677-5788 6261-6349 6384-6753 6814-6902
HADDB75	31	757028	AC006405	1020	1-852 2867-2974 3284-3395 7046-7165 7495-7669 7707-8244 8499-8610 9206-9575 9636-9724 10892-11305 11498-11601 13245-13564 15626-15761 16264-16363 17246-17403 18613-18793 19923-20414 20563-20671 20852-22161
HADDB75	31	757028	AC068936	1021	1-414
HADDB75	31	757028	AC006405	1022	1-2826 3446-3608
HADDB75	31	757028	AC006405	1023	1-96

HADDC66	32	787301	AL049563	1024	1-643
HADDC66	32	787301	AL049563	1025	1-363
HADDC66	32	787301	AL049563	1026	1-330
HADEU56	36	733346	AC017092	1027	1-337 392-1302
HADEU56	36	733346	AC011794	1028	1-337 392-1302
HADEU56	36	733346	AC008513	1029	1-337 392-1302
HADEU56	36	733346	AC011794	1030	1-153
HADFX30	38	970565	AC011498	1031	1-603
HADFX30	38	970565	AC011498	1032	1-247
HADFX30	38	970565	AC011498	1033	1-252
HADFX35	39	675830	AL139808	1034	1-1361
HADFX35	39	675830	AL136368	1035	1-1808
HADFX35	39	675830	AL158163	1036	1-1808
HADFX35	39	675830	AL136368	1037	1-338
HADFX35	39	675830	AL136368	1038	1-293
HADFX35	39	675830	AL158163	1039	1-293
HADFX35	39	675830	AL158163	1040	1-338
HADGA36	40	705766	AL022315	1041	1-104 2082-2927 4315-4441 5256-5330 5585-6331 7626-8923
HADGA36	40	705766	AL022315	1042	1-945
HADGD54	41	729761	AL356000	1043	1-569 827-1480 1542-1854 2049-4571
HADGD54	41	729761	AC024502	1044	1-190 2311-2654 2971-3108 4195-4501 4743-5311 5569-6222 6284-6596 6791-10462
HADGD54	41	729761	AC024502	1045	1-298
HADGE37	42	744768	AC018653	1046	1-390 712-886 1163-1428 1737-1883 2118-3268 7117-7225 7626-8121

					8681-8881 9131-10138
HADGE37	42	744768	AC018653	1047	1-154
HADXA61	44	741926	AC010402	1048	1-288
HADXA61	44	741926	AC008920	1049	1-135 1530-1670 2247-2534 2735-3065 3233-3367 4240-4407 6282-6385
HADXA61	44	741926	AC010402	1050	1-331
HARMG09	45	705996	AC069168	1051	1-412
HARMG09	45	705996	AC023672	1052	1-412
HARMG09	45	705996	AC023672	1053	1-447
HARMG60	46	933284	AC019300	1054	1-552
HARMG60	46	933284	AC025821	1055	1-552
HARMM43	47	714763	AL355773	1056	1-854 2013-2134 2650-3156 3284-3379 3563-3826 4498-4620 5597-5673 7008-7286 7721-8002 8099-8648 9030-9519
HARMM43	47	714763	AL138499	1057	1-74 1171-1414 2003-2145 5281-5390 6571-6708 7273-8042 8498-8581 9242-9411 9823-9893 11229-11269 11959-12050 12418-12490 12981-13017 13172-13255 13739-13807 16333-16490 16856-16966 17025-17457 19018-19053

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HARMM43	47	714763	AL138499	1058	1-386 635-1149

HARMP39	48	705255	AL356597	1059	1-574
HARMP39	48	705255	AL356597	1060	1-254
HARMP42	49	713247	AC009884	1061	1-524
HARMS39	50	933273	AC068789	1062	1-117 1201-1235 2649-2755 3094-3186 3195-3768
HARMS39	50	933273	AC025570	1063	1-332
HARMS39	50	933273	AC025686	1064	1-117 1203-1237 2651-2757 3096-3188 3197-3770
HARMS77	51	752659	AC005104	1065	1-384
HARMS77	51	752659	AC005104	1066	1-155
HARMS77	51	752659	AC005104	1067	1-2931
HARMU03	52	923179	AC025861	1068	1-184
HARMU03	52	923179	AC067825	1069	1-567
HARMU03	52	923179	AL353794	1070	1-590
HARMU03	52	923179	AL353791	1071	1-576
HARMU03	52	923179	AL353729	1072	1-576
HARMU03	52	923179	AL353791	1073	1-267 822-968 2514-2795
HARMU03	52	923179	AL353791	1074	1-308
HARMU03	52	923179	AL353729	1075	1-205 757-1091 1333-1635
HARNC40	55	710613	AL359396	1076	1-678
HARND80	56	864604	AP001459	1077	1-575 908-1384 2117-2230 2335-2475 2884-2941 3046-3263 3879-4131 4477-4739 7651-7883 8062-8168 8498-8642 8740-8974
HARND80	56	864604	AP001362	1078	1-140 549-606 711-928 1541-1988 2142-2404

					5317-5549 5728-5834 6164-6308 6406-6640
HARND80	56	864604	AC022488	1079	1-99 435-525 680-793 918-1021 1162-1255 1415-1567 1983-2557 2891-3364 4092-4205 4310-4450 4858-4915 5021-5237 5851-6785 7133-7163 9614-9843 10020-10125 10452-10596 10692-10923
HARND80	56	864604	AP001459	1080	1-248 616-1133 1206-1886
HARND80	56	864604	AP001362	1081	1-248 616-1135
HARND80	56	864604	AC022488	1082	1-353
HARND80	56	864604	AC022488	1083	1-228 595-1111 1184-1700 1702-1847
HARNH52	58	726277	AL359749	1084	1-354
HARNO29	59	690043	AP000794	1085	1-254
HARNO29	59	690043	AP000794	1086	1-441
HAWAD93	60	508724	AL160159	1087	1-60 115-481
HAWAD93	60	508724	AL354927	1088	1-60 115-481
HAWAD93	60	508724	AL160159	1089	1-253
HAWAD93	60	508724	AL354927	1090	1-253
HAWAP49	61	537199	AL109741	1091	1-558 683-2946 3005-4063
HAWAP49	61	537199	AL161741	1092	1-2264 2323-3381
HAWAP49	61	537199	AL109741	1093	1-589

HAWAP49	61	537199	AL161741	1094	1-589
HBIMG05	62	930827	AC013648	1095	1-388 711-1430 2248-2407
HBIMG05	62	930827	AC013648	1096	1-427
HBIMG05	62	930827	AC013648	1097	1-82 562-616 2402-2542 4845-4949
HBIMS01	63	913827	AL158049	1098	1-816
HBIMS01	63	913827	AL158049	1099	1-977
HBIMS01	63	913827	AL158049	1100	1-549
HBIOO63	64	969020	AC068451	1101	1-325 1063-2934 2956-3637 3643-3941 4592-5386 5463-5530
HBIOO63	64	969020	AC068451	1102	1-290
HBIOP02	65	918022	AC068266	1103	1-138
HBIOP02	65	918022	AC068266	1104	1-638
HBIOP02	65	918022	AC068266	1105	1-762
HBIOS05	66	930776	AL355480	1106	1-695 736-1435 1556-1637 1721-1841 2042-2147 2393-2720
HBIOS05	66	930776	AL355480	1107	1-209 279-391 671-1068
HBIOS05	66	930776	AL355480	1108	1-202
HERAC92	69	973454	AC023498	1109	1-611 1707-1777 2285-2396 3594-3899 3993-4026 4102-4259 4318-4819 6094-6191
HERAC92	69	973454	AC010198	1110	1-611 1711-1781 2289-2400 3598-3903 3997-4030 4106-4263 4322-4823

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HERAC92	69	973454	AC023498	1111	1-301
HERAC92	69	973454	AC023498	1112	1-300
HERAC92	69	973454	AC010198	1113	1-301
HERAD10	71	973489	AC068122	1114	1-375
HERAD10	71	973489	AL359089	1115	1-375
HERAD10	71	973489	AL359089	1116	1-407
HERAG57	73	973668	AC034237	1117	1-52 1051-1343 2584-2859
HERAG57	73	973668	AC021463	1118	1-291
HERAG57	73	973668	AC021463	1119	1-106
HERAJ78	74	973676	AC009949	1120	1-848
HERAM84	76	529193	AC025977	1121	1-282 2534-2803 3379-3590
HERAM84	76	529193	AC040170	1122	1-282 2533-2802 3378-3589
HERAM84	76	529193	AC013513	1123	1-270
HERAM84	76	529193	AC013513	1124	1-166
HESAD92	79	537451	AC008695	1125	1-773
HESAD92	79	537451	AC005218	1126	1-773
HESAD92	79	537451	AC008695	1127	1-774
HESAD92	79	537451	AC005218	1128	1-774
HESAT22	80	537449	AC016585	1129	1-328
HESAT22	80	537449	AC026467	1130	1-327
HESAT88	81	537446	AL138709	1131	1-222
HFEAG37	82	705454	Z99289	1132	1-1153 1168-1755 3469-3564 3581-4021 5066-5224 7327-7437 8691-8829 9049-9279 12124-12616 12725-12932
HFEAH35	83	504585	AL132987	1133	1-126 766-1274 2042-2684 3419-3542 4713-4919 7711-8106 8844-9165 9416-9587 11482-11779

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HFEAH35	83	504585	AL132987	1134	1-383
HFEAH35	83	504585	AL132987	1135	1-475
HFEAN02	84	932828	AL133294	1136	1-278
HFEAN02	84	932828	AL133294	1137	1-509
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HFEAN43	85	524355	AL391069	1139	1-384
HFEAQ11	87	530368	AL356867	1140	1-468 657-866 1115-1736
HFEAS89	88	960624	AC068117	1141	1-132 695-848 1047-1180 2087-2192 2278-2591 3580-3684 4418-4622
HFEAS89	88	960624	AC068117	1142	1-486
HFEBG06	93	935683	AC055807	1143	1-368 430-1049
HFEBL88	94	766085	AC021165	1144	1-223 332-2006
HFEBL88	94	766085	AC022435	1145	1-2423
HFEBL88	94	766085	AC010454	1146	1-2428
HFEBL88	94	766085	AC024592	1147	1-2426
HFEBL88	94	766085	AC022435	1148	1-89
HKABE64	98	879492	AC018629	1149	1-74 2195-2617 3133-3573 5088-5526
HKABE64	98	879492	AC018629	1150	1-344
HKACL95	102	973360	AL050402	1151	1-427
HKACL95	102	973360	AL050402	1152	1-155
HKACM63	103	952653	AP000920	1153	1-67 4967-5603 5625-5938
HKACM63	103	952653	AP000920	1154	1-85

HKACU93	104	908022	AC008620	1155	1-558 2623-2750 3090-3275 3856-3989 6489-6581 6895-7342 7704-8026 8401-8629 9153-11553
HKACU93	104	908022	AC008620	1156	1-446
HKADP74	107	765535	AC005726	1157	1-138 399-526 4423-4719 5965-7053 7162-7338 8147-8288 12535-12611 12852-12945 13035-13174 13383-13504 13623-13716 13815-13935 14288-14383 14553-14705 14783-14885 15047-16061 18915-19026 19198-19284 19547-19675 19780-19904 20281-21470
HKADP74	107	765535	AC005726	1158	1-128 902-959 1377-1507 1586-1806 1916-1985 2055-2231 2338-2433 2681-2871 2977-3198 3300-3809
HKAEC04	108	857355	AC067749	1159	1-81 610-1275 1444-1660 1750-2267 2590-3070 3195-3769

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HKAEC04	108	857355	AC067749	1160	1-360
HKAEE60	109	812691	AL158217	1161	1-945 1211-1640 2048-2161 2383-3444 4592-4710 5395-5629 5953-6265
HKAEE60	109	812691	AL031848	1162	1-945 1211-1640 2047-3444 4592-4710 5078-5201 5395-5629
HKAEE60	109	812691	AL158217	1163	1-43 77-198
HKAEE60	109	812691	AL031848	1164	1-313
HKAEV94	111	973353	AC018662	1165	1-372
HKAEV94	111	973353	AC008039	1166	1-372
HKAEV94	111	973353	AC018662	1167	1-164
HKAEV94	111	973353	AC008039	1168	1-164
HKAFO42	113	713722	AC024400	1169	1-616
HKAFO42	113	713722	AC024400	1170	1-635
HKAFO42	113	713722	AC022059	1171	1-1250 1310-2528
HKAFO42	113	713722	AC022059	1172	1-842
HKAHF84	115	887386	AC024085	1173	1-65 3759-4150 5563-5643 6086-6223 7197-7422 7635-7683
HKAHF84	115	887386	AC024085	1174	1-106
HKAHF84	115	887386	AC024085	1175	1-343
HKAIF25	118	974416	AL136293	1176	1-295 982-1082 2381-3243
HKAIF25	118	974416	AL136293	1177	1-119
HKAIF12	119	893937	AL157697	1178	1-286
HKAIF12	119	893937	AL035588	1179	1-292
HKAIF12	119	893937	AL035588	1180	1-313
HKAJG02	121	857330	AC073984	1181	1-1483

HKAKI80	124	973231	AC004991	1182	1-538 566-715 1576-1985 4789-4988 7590-7740 7760-8055 8147-8297 8594-9056 10201-10256
HKAKI80	124	973231	AC004991	1183	1-119 768-1002 1546-1672
HKAKP85	126	927032	AL138898	1184	1-443
HKAKP85	126	927032	AL138898	1185	1-323
HKAKP85	126	927032	AL138898	1186	1-484
HKAOE10	127	963543	AC013416	1187	1-84 546-731 872-1686 2025-2959 2986-3171 4525-4666 5789-6100 7377-7730 7835-7896 7898-8202 8575-9161 9545-9656 9828-10129 10326-10506 11861-12555
HKAOE10	127	963543	AC013416	1188	1-261
HKAOM71	128	761303	AL139013	1189	1-536
HKAOM71	128	761303	AL354953	1190	1-536
HKAOM71	128	761303	AL139013	1191	1-443
HKAOM71	128	761303	AL354953	1192	1-443
HKAPN78	131	973220	AC009172	1193	1-770
HKAPN78	131	973220	AC007598	1194	1-767
HKAPN78	131	973220	AC007612	1195	1-767
HKAPN78	131	973220	AC009172	1196	1-760
HKAPN78	131	973220	AC007598	1197	1-760 841-1311 1676-2080 4416-5080
HKAPN78	131	973220	AC007612	1198	1-760 841-1311 1676-2080 4416-5080

HOUCL76	134	531425	AC016824	1199	1-299
HOUCL76	134	531425	AC023906	1200	1-299
HOUCL76	134	531425	AC016824	1201	1-299
HOUCL76	134	531425	AC023906	1202	1-212
HOUCR21	135	936034	AL356221	1203	1-107 764-1342 1998-2170 3272-3324 3873-4255
HOUCR21	135	936034	AC068053	1204	1-107 763-1341 1997-2169 3271-3323 3872-4254
HOUCR21	135	936034	AC068053	1205	1-251
HOUCR21	135	936034	AL356221	1206	1-562
HOUCS91	138	526717	AL158152	1207	1-6049 8437-9272 9371-9523 11900-12703 13529-13693 14081-14437 15219-15333 16106-16532 16785-16930 18772-20802 21278-21497 22261-22609 24440-30515
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HKAGC23	322	912677	AL158167	1579	1-133 1297-1410 3430-3888 5807-5860 6668-6762 8151-8717 10593-10879 10939-12822
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HADEU65	440	747880	AC024649	1839	1-1136
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HADDE15	453	952542	AC018606	1901	1-160 763-1583 1988-2201
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HADDB62	459	743476	AC024357	1909	1-457
HADDB13	460	657120	AC016722	1910	1-456
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HADCW01	464	916399	AC012431	1918	1-412 810-1279 1502-1630 2316-2382 3130-4418
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HADCP50	466	723684	AC018645	1925	1-434
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HADCN29	469	690600	AC055747	1934	1-1617
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HADAY29	472	690602	AL133326	1943	1-332
HADAY29	472	690602	AL133326	1944	1-6053
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HADAR23	474	675844	AL161618	1946	1-935
HADAR23	474	675844	AL096772	1947	1-935
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HADAM60	475	740326	AL138803	1950	1-615
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HADAE96	476	796469	AL157858	1954	1-434 439-1127 1277-1385 1430-2038 2086-2687
HADAE96	476	796469	AL157858	1955	1-235
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HACCT11	479	966886	AC027793	1959	1-490
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					22601-23557 24423-24723 25467-25997 26019-26210
HACBW76	480	849054	AC010480	1967	1-530
HACBW76	480	849054	AC020728	1968	1-291
HACBW76	480	849054	AC010480	1969	1-310
HACBW76	480	849054	AC020728	1970	1-530
HACBU26	481	683006	AL157395	1971	1-1377 1831-4672
HACBU26	481	683006	AL157395	1972	1-552
HACBU26	481	683006	AL157395	1973	1-216
HACBN71	483	872015	AC018782	1974	1-1224 1463-2010 2048-2174 3135-3512
HACBN71	483	872015	AC018782	1975	1-129
HACBN71	483	872015	AC018782	1976	1-460 1163-1593 1644-1768 1797-1903 2271-2568 2604-2981 3064-3236 4035-4230 4840-4920 5012-5119 5352-5387 7427-7588 7851-8701
HACBJ83	484	875263	AL158839	1977	1-283
HACBJ83	484	875263	AL158839	1978	1-1912
HACBJ83	484	875263	AL158839	1979	1-346
HACBJ17	485	663371	AL356577	1980	1-1536
HACBJ17	485	663371	AL049713	1981	1-1536
HACBJ17	485	663371	AL356577	1982	1-185
HACBJ17	485	663371	AL049713	1983	1-185
HACBB13	487	698800	AC044881	1984	1-1106 1288-1949 2100-3536
HACBB13	487	698800	AC026291	1985	1-1106 1289-1950 2095-3530
HACBB13	487	698800	AC026291	1986	1-501
HACAB93	488	792382	AC073585	1987	1-1886
HACAB93	488	792382	AC073585	1988	1-612
HACAA57	489	733887	AC027384	1989	1-403

					415-914 956-1508
HACAA57	489	733887	AL357732	1990	1-403 415-914 956-1508
HACAA57	489	733887	AL356429	1991	1-405 417-916 958-1510
HACAA57	489	733887	AC073499	1992	1-403 415-914 956-1508
HACAA57	489	733887	AL356429	1993	1-530
HACAA57	489	733887	AC027384	1994	1-530
HACAA57	489	733887	AL357732	1995	1-530
HACAA57	489	733887	AC073499	1996	1-530
HACAA03	490	924513	AC016684	1997	1-656
HACAA03	490	924513	AC020901	1998	1-1189
HACAA03	490	924513	AC026427	1999	1-656
HACAA03	490	924513	AC010248	2000	1-1183
HABGA24	491	676827	AL121926	2001	1-203 1830-1953 2743-2933 3071-3533 4061-4265 5066-5270 5371-6058 6482-6626 6816-6942 7029-7116 7408-7737
HABGA24	491	676827	AL121926	2002	1-101
HABGA24	491	676827	AL121926	2003	1-463

[056] Table 1B summarizes additional polynucleotides encompassed by the invention (including cDNA clones related to the sequences (Clone ID NO:Z), contig sequences (contig identifier (Contig ID:) contig nucleotide sequence identifiers (SEQ ID NO:X)), and genomic sequences (SEQ ID NO:B). The first column provides a unique clone identifier, "Clone ID NO:Z", for a cDNA clone related to each contig sequence. The second column provides the sequence identifier, "SEQ ID NO:X", for each contig sequence. The third column provides a unique contig identifier, "Contig ID:" for each contig sequence. The fourth column, provides a BAC identifier "BAC ID NO:A" for the BAC clone referenced in the corresponding row of the table. The fifth column provides the nucleotide sequence identifier, "SEQ ID NO:B" for a fragment of the BAC clone identified in column four of the corresponding row of the table. The sixth column, "Exon From-To", provides the location (i.e., nucleotide position numbers) within the polynucleotide sequence of SEQ ID NO:B which delineate certain polynucleotides of the invention that are also exemplary members of polynucleotide sequences that encode polypeptides of the invention (e.g., polypeptides containing amino acid sequences encoded by the polynucleotide sequences delineated in column six, and fragments and variants thereof).

TABLE 2

Clone ID NO:Z	Contig ID:	SEQ ID NO:X	Analysis Method	PFam/NR Description	PFam/NR Accession Number	Score/ Percent Identity	NT From	NT To
HACAD23	926345	12	blastx.2	(AF123591) fertilization envelope outer layer protein [Cyprinus carpio]	gb AAD23572.1 AF1 23591_1	40% 52%	75 373	413 441
HACAD23	926346	492	blastx.14	VMO-I [Gallus gallus]	gi 487906 dbj BAA05 086.1	46% 58% 66%	97 298 175	174 333 201
HACBA49	722875	14	blastx.2	(AE000303) orf, hypothetical protein [Escherichia coli]	gb AAC75206.1	60%	426	214
HADCK83	609846	20	blastx.2	(AF010144) neuronal thread protein AD7c-NTP [Homo sapiens]	gb AAC08737.1	74% 76% 86%	597 585 446	424 436 402
HADCQ37	970564	27	blastx.2	(AF064748) S3-12 [Mus musculus]	gb AAC23666.1	55% 55% 54% 53% 54% 51% 53% 50% 54% 53% 50% 53% 51% 53% 52%	56 56 56 56 56 56 56 56 56 56 56 56 53 56	547 547 547 547 547 586 547 586 547 547 586 547 547 547 547

						56	523
						56	586
						56	586
						53	586
						56	547
						56	586
						56	547
						56	586
						56	586
						56	526
						143	547
						56	418
						56	415
						56	418
						499	711
						517	711
						517	711
						493	711
						493	711
						517	696
						517	711
						517	696
						517	696
						517	696
						517	696
						517	696
						517	711
						517	696
						517	696

HADCU18	666360	28	blastx.2	(AF064748) S3-12 [Mus musculus]	gb AAC23666.1	40%	517	711
HADDF89	786876	34	blastx.2	(AK000496) unnamed protein product [Homo sapiens]	dbj BAA91205.1	78%	517	696
HADDQ25	849002	35	blastx.2	(AF090942) PRO0657 [Homo sapiens]	gb AAF24054.1 AF090942_1	65%	374	279
HADFG58	727536	37	blastx.2	zinc finger protein [Homo sapiens]	gb AAA59469.1	65%	210	296
HADFX35	675830	39	blastx.2	(AK000496) unnamed protein product [Homo sapiens]	dbj BAA91205.1	65%	353	171
HADGR61	848971	43	blastx.2	(AJ223366) hypothetical protein [Homo sapiens]	emb CAB65727.1	85%	210	368
HARND80	864604	56	blastx.2	(AF096286) pecanex 1 [Mus musculus]	gb AAF21809.1 AF096286_1	97%	2	124
HBIOS05	930776	66	HMMER 1.8	PFAM: Zinc finger, C2H2 type	PF00096	45%	109	213
						58%	47	82
						78%	30	572
						10.54	168	230

HERAC92	973454	69	blastx.2	(AK000385) unnamed protein product [Homo sapiens]	dbj BAA91131.1	61% 90%	503 367	387 305
HERAJ78	973676	74	blastx.2	reverse transcriptase [Homo sapiens]	gb AAB02291.1	44%	84	494
HFEAN43	524355	85	blastx.2	(AF161356) HSPC093 [Homo sapiens]	gb AAF28916.1 AF161356_1	41% 64%	100 71	285 121
HFEAO67	954402	86	blastx.2	similar to Schizosaccharomyces pombe cut1+ protein which 1	dbj BAA11482.1	84%	15	344
HFEBB35	974535	90	blastx.2	(AL096881) hypothetical protein [Homo sapiens]	emb CAB51405.1	68%	58	306
HKAAU11	966953	97	blastx.2	(AF198489) LBP-32 [Homo sapiens]	gb AAF32276.1 AF198489_1	62%	179	397
HKABR48	702372	99	blastx.2	(AK000207) unnamed protein product [Homo sapiens]	dbj BAA91009.1	35%	321	821
HKACU93	908022	104	blastx.2	(AF156272) RING finger protein terf [Rattus norvegicus]	gb AAD40287.1	26% 57% 48% 38%	62 3 438 21	436 101 530 74
HKADC82	944994	106	blastx.2	(AF155511) KX antigen [Mus musculus]	gb AAF14527.1 AF155511_1	30% 47%	188 3	526 185
HKADP74	765535	107	blastx.2	(AF063308) coiled-coil related protein DEEPEST [Homo sapiens]	gb AAD02813.1	68%	90	548
HKAFO42	713722	113	blastx.2	(AF118082) PRO1902 [Homo sapiens]	gb AAF22026.1 AF118094_21	65% 52%	2 79	79 135

HKAHF84	887386	115	blastx.2	(AF095719) carboxypeptidase A3 [Homo sapiens]	gb AAF23230.1 AF0 95719_1	96%	3	329
HKAJW52	836587	123	blastx.2	(AF154107) UDP- GalNAc:polypeptide 1	gb AAF15313.1 AF1 54107_1	100%	16	171
HKAOE10	963543	127	blastx.2	(AF090931) PRO0483 [Homo sapiens]	gb AAF24046.1 AF0 90931_1	65%	109	5
HKAON82	779247	129	blastx.2	(AL030998) dJ46618.1 (Coagulation Factor V (Activated Protein 1 1	emb CAA19742.1	55% 43%	402 402	154 154
HKAPN78	973220	131	blastx.2	(AK000385) unnamed protein product [Homo sapiens]	dbj BAA91131.1	67%	274	56
HOUCS91	526717	138	blastx.2	(AF090930) PRO0478 [Homo sapiens]	gb AAF24045.1 AF0 90930_1	79%	250	351
HOUDX25	524248	142	blastx.2	(AE000218) orf, hypothetical protein [Escherichia coli]	gb AAC74280.1	100% 89%	146 61	241 144
HOUFB87	837251	144	blastx.2	(AK000496) unnamed protein product [Homo sapiens]	dbj BAA91205.1	67%	690	430
HOUFZ64	750784	151	blastx.2	(AK001264) unnamed protein product [Homo sapiens]	dbj BAA91588.1	93%	3	98
HSTAZ54	508368	171	blastx.2	(AK001797) unnamed protein product [Homo sapiens]	dbj BAA91917.1	94%	232	336
HSTBC04	506961	172	blastx.2	ranbp3-a [Homo sapiens]	emb CAA69956.1	100%	128	289
HWDAO26	679520	179	blastx.2	cysteine rich hair keratin	emb CAA56339.1	35%	143	400

[illegible]

HWJAC59	761620	213	HMMER 1.8	PFAM: Core histones H2A, H2B, H3 and H4	PF00125	10.11	47	106
HWHQL26	694021	221	blastx.2	zinc finger=ZNF126 [human, Peptide Partial, 98 aa] [Homo sapiens]	gb AAB24881.1	50% 45%	142 257	246 322
HWHPO68	752782	228	blastx.2	(AB026833) chloride channel protein [Homo sapiens]	dbj BAA77810.1	90% 100%	126 1	497 126
HWHPK51	725456	232	blastx.2	(AK001660) unnamed protein product [Homo sapiens]	dbj BAA91819.1	96% 100%	156 251	245 289
HWHGY56	733124	249	blastx.2	(AL080149) hypothetical protein [Homo sapiens]	emb CAB45742.1	79% 69% 100%	77 285 3	253 398 23
HWHGW72	945692	250	HMMER 2.1.1	PFAM: ATP P2X receptor	PF00864	438.5	247	855
			blastx.2	(AF190822) P2X2A receptor [Homo sapiens]	gb AAF19170.1 AF1 90822_1	91%	190	939
HWHGF95	947019	253	HMMER 1.8	PFAM: Trypsin	PF00089	309.92	56	724
			blastx.2	(AF135026) kallikrein- like protein 3 KKL-L3 [Homo sapiens]	gb AAD26427.2 AF1 35026_1	93%	35	742
HWHGE01	915933	254	blastx.2	(AK001510) unnamed protein product [Homo sapiens]	dbj BAA91730.1	100%	2	280
HWHGC57	942388	256	HMMER 1.8	PFAM: Cadherin	PF00028	40.03	59	253
			blastx.2	(AK000054) unnamed	dbj BAA90911.1	39%	71	499

				protein product [Homo sapiens]			36%	122	409
HWHGB85	889955	257	blastx.2	(AF161511) HSPC162 [Homo sapiens]	gb AAF29126.1 AF161511.1	98%	385	618	
HWFBB09	575533	262	blastx.2	(AF118082) PRO1902 [Homo sapiens]	gb AAF22026.1 AF118094.21	63%	3	158	
HWFAD84	504489	264	blastx.2	(AK002129) unnamed protein product [Homo sapiens]	dbj BAA92096.1	70%	152	262	
HWDAY07	952441	268	blastx.2	(AF174605) F-box protein Fbx25 [Homo sapiens]	gb AAF04526.1 AF174605.1	96%	285	995	
HWIDAS21	670233	269	blastx.2	repressor transcriptional factor [Homo sapiens]	gb AAA79179.1	48%	516	1	
						53%	516	88	
						50%	516	88	
						58%	516	169	
						59%	516	175	
						56%	516	169	
						51%	516	88	
						48%	516	94	
						51%	516	88	
						56%	516	175	
						50%	516	151	
						56%	516	187	
						49%	516	175	
						41%	450	88	
						29%	498	88	
HWDAD40	881233	277	blastx.2	(AK000284) unnamed	dbj BAA91053.1	98%	445	293	

				protein product [Homo sapiens]					
HSTAO59	908993	279	HMMER 2.1.1	PFAM: Zinc finger, C2H2 type	PF00096	55.2	271	339	
			blastx.2	Zfp64 [Mus musculus]	gb AAC53039.1	78%	1	342	
						40%	10	339	
						42%	58	342	
						40%	64	333	
						36%	1	333	
						35%	1	339	
						65%	329	442	
						38%	356	433	
						41%	353	424	
						29%	353	424	
						30%	103	186	
HSTAH84	783227	280	blastx.2	Pro-Pol-dUTPase polypeptide [Mus musculus]	emb CAA73251.1	40%	11	226	
						50%	231	335	
						70%	296	355	
HOUET93	792495	291	blastx.2	(AE000413) putative amino acid/amine transport protein [Escherichia coli]	gb AAC76395.1	85%	20	202	
HOUK01	965449	295	blastx.2	(AL049730) putative protein [Arabidopsis thaliana]	emb CAB53752.1	66%	469	293	
						54%	515	450	
HOUADR29	576473	298	blastx.2	(AF090944) PRO0663 [Homo sapiens]	gb AAF24056.1 AF090944_1	86%	176	66	
HOUADR25	559993	301	blastx.2	put. ORF [Homo sapiens]	emb CAA39297.1	58%	46	204	
HOUAF65	526540	306	blastx.2	(AK000844) unnamed protein product [Homo sapiens]	dbj BAA91396.1	66%	58	165	

HLIBE40	887417	311	blastx.2	sapiens] (AF067660) Bcl-2 homolog [Mus musculus]	gb AAC83150.1	64% 35% 42%	318 136 77	434 339 139
HKAOO90	934020	313	blastx.2	(AK001750) unnamed protein product [Homo sapiens]	dbj BAA91881.1	81%	3	629
HKAJK82	779306	317	blastx.2	(AF161356) HSPC093 [Homo sapiens]	gb AAF28916.1 AF1 61356_1	64% 69% 58%	355 559 500	471 597 550
HKAHI69	916528	319	blastx.2	(AF083110) sirtuin type 5 [Homo sapiens]	gb AAD40853.1 AF0 83110_1	73%	272	634
HKAHA10	857339	321	blastx.2	(AK001527) unnamed protein product [Homo sapiens]	dbj BAA91741.1	59% 59% 42%	19 192 242	195 272 325
HKAGC23	912677	322	blastx.2	rab18 [Mus musculus]	emb CAA56583.1	97%	69	170
HKAFD03	924048	326	blastx.2	(AF113685) PRO0974 [Homo sapiens]	gb AAF29584.1 AF1 13685_1	49%	519	319
HKAEG61	925951	328	HMMER 1.8 blastx.2	PFAM: Laminin B (Domain IV) Eps8 [Mus musculus]	PF00052	0.46	343	278
HKADR84	800106	329	blastx.2	(AK002148) unnamed protein product [Homo sapiens]	gb AAA16358.1 dbj BAA92109.1	44% 36% 97%	348 449 172	118 342 279
HKADP50	971356	330	HMMER 2.1.1 blastx.2	PFAM: PLAT/LH2 domain lipoxigenase-3 [Mus musculus]	PF01477 emb CAB46101.1	108.4 86% 81%	291 288 736	635 668 1089

HKADO84	911567	332	blastx.2	(AL117537) hypothetical protein [Homo sapiens]		emb CAB55983.1	81% 37% 61% 48%	668 853 1094 4	748 939 1147 252
HKACP23	881718	339	blastx.2	(AK000363) unnamed protein product [Homo sapiens]		dbj BAA91112.1	77%	3	431
HKACO69	614156	340	blastx.2	(AF037261) SH3-containing adaptor molecule-1 [Homo sapiens]		gb AAC09244.1	74% 78%	106 9	303 65
HKACL83	881711	342	blastx.2	actin filament protein [Gallus gallus]		gb AAA67326.1	57% 58%	4 481	318 573
HFEBJ61	576092	356	blastx.2	reverse transcriptase [Peromyscus leucopus]		gb AAC64414.1	56% 51% 50% 36%	211 74 326 153	321 154 355 209
HFEAJ78	855319	362	blastx.2	(AF010144) neuronal thread protein AD7c-NTP [Homo sapiens]		gb AAC08737.1	69%	498	352
HFEAI49	722129	364	blastx.2	keratin type I [Homo sapiens]		emb CAA76386.1	100%	1	105
HERAS69	974532	370	blastx.2	unknown protein [Homo sapiens]		gb AAA88036.1	42% 66% 26% 40%	369 482 199 233	229 447 122 189
HERAH85	928415	380	blastx.2	(AK000385) unnamed protein product [Homo sapiens]		dbj BAA91131.1	78% 84%	185 321	337 419

HERAD26	520370	388	blastx.2	(AF090895) PRO0117 [Homo sapiens]	gb AAF24019.1 AF090895_1	76% 66%	63 316	188 342
HBIOZ10	973131	393	HMMER 1.8	PFAM: Eukaryotic protein kinase domain	PF00069	121.1	3	365
			blastx.2	(AF003134) strong similarity to the CDC2/CDX subfamily of ser/thr protein kinases [Caenorhabditis elegans]	gb AAB54139.1	60%	3	305
HBIOM94	973137	396	HMMER 2.1.1	PFAM: Ank repeat	PF00023	37.4	476	574
			blastx.2	contains 10 ankyrin-like repeats; similar to human ankyrin, 1 bursaria Chlorella virus 1]	gb AAC96986.1	33% 31% 25% 29%	479 291 786 285	757 482 962 467
HAWAY15	829255	405	blastx.2	(AK001675) unnamed protein product [Homo sapiens]	dbj BAA91828.1	98% 66% 100%	130 78 70	363 113 90
			blastx.2	zinc finger protein [Rattus norvegicus]	emb CAA42610.1	96% 82% 80%	188 1 426	427 123 515
HADFW06	935340	429	blastx.2	(AF118082) PRO1902 [Homo sapiens]	gb AAF22026.1 AF118094_21	64% 73%	172 228	5 172
HADFD69	754277	434	blastx.2	(AF155115) NY-REN-58 antigen [Homo sapiens]	gb AAD42881.1 AF155115_1	88%	1	459
HADFB60	740318	436	blastx.2	(AF036705) Similar to phytoene desaturase; coded for by C. 1.1 cDNA yk303f4.5; coded for by C. elegans cDNA	gb AAB95172.1	59% 64%	190 395	411 433

HADFB08	959273	438	HMMER 1.8	yk257d4.5; coded for PFAM: Src homology domain 3	PF00018	2.83	158	202
HADET68	906389	442	blastx.2	EGF repeat transmembrane protein [Mus musculus]	gb AAB01338.1	92% 54%	768 169	655 137
HADDS21	670802	444	blastx.2	ZZ:beta-Gal' IgG-binding fusion protein [unidentified cloning 1]	gb AAB00807.1	95%	86	226
HADDS07	849000	445	blastx.2	(AF113685) PRO0974 [Homo sapiens]	gb AAF29584.1 AF1 13685_1	54% 70% 57%	49 234 24	231 305 80
HADDI89	865278	449	blastx.2	(AF118086) PRO1992 [Homo sapiens]	gb AAF22030.1 AF1 18094_25	77% 78%	14 184	67 225
HADDE15	952542	453	blastx.2	(AC018849) putative N- terminal acetyltransferase [Arabidopsis thaliana]	gb AAF27136.1 AC0 18849_24	46%	17	715
HADCZ08	959304	462	blastx.2	(AK002129) unnamed protein product [Homo sapiens]	dbj BAA92096.1	73%	252	365
HACBW76	849054	480	blastx.2	(AF161356) HSPC093 [Homo sapiens]	gb AAF28916.1 AF1 61356_1	45% 44%	404 498	225 397
HACBU26	683006	481	blastx.2	(AF083384) 45kDa splicing factor; SPF 45 [Homo sapiens]	gb AAC64085.1	100% 88%	194 545	409 652
HACBJ83	875263	484	blastx.2	(AF126164) alternative HHLA3 protein [Homo sapiens]	gb AAD33289.1 AF1 26164_1	77%	126	350
HACBH42	933951	486	blastx.2	(AF124251) SH2-	gb AAD28246.1 AF1	54%	47	427

				containing protein Nsp3 [Homo sapiens]	24251_1	100%	1	51
HACBB13	698800	487	blastx.2	(AK001782) unnamed protein product [Homo sapiens]	dbj BAA91907.1	78%	425	216
HABGA24	676827	491	blastx.2	(AJ245600) hypothetical protein [Homo sapiens]	emb CAB53247.1	98%	17	175

[057] Table 2 further characterizes certain encoded polypeptides of the invention, by providing the results of comparisons to protein and protein family databases. The first column provides a unique clone identifier, "Clone ID NO:", corresponding to a cDNA clone disclosed in Table 1A. The second column provides the unique contig identifier, "Contig ID:" which allows correlation with the information in Table 1A. The third column provides the sequence identifier, "SEQ ID NO:X", for the contig polynucleotide sequences. The fourth column provides the analysis method by which the homology/identity disclosed in the row was determined. The fifth column provides a description of PFam/NR hits having significant matches identified by each analysis.

Column six provides the accession number of the PFam/NR hit disclosed in the fifth column. Column seven, "Score/Percent Identity", provides a quality score or the percent identity, of the hit disclosed in column five. Comparisons were made between polypeptides encoded by polynucleotides of the invention and a non-redundant protein database (herein referred to as "NR"), or a database of protein families (herein referred to as "PFam"), as described below.

[058] The NR database, which comprises the NBRF PIR database, the NCBI GenPept database, and the SIB SwissProt and TrEMBL databases, was made non-redundant using the computer program nrdb2 (Warren Gish, Washington University in Saint Louis). Each of the polynucleotides shown in Table 1A, column 3 (e.g., SEQ ID NO:X or the 'Query' sequence) was used to search against the NR database. The computer program BLASTX was used to compare a 6-frame translation of the Query sequence to the NR database (for information about the BLASTX algorithm please see Altshul et al., J. Mol. Biol. 215:403-410 (1990), and Gish et al., Nat. Genet. 3:266-272 (1993)). A description of the sequence that is most similar to the Query sequence (the highest scoring 'Subject') is shown in column five of Table 2 and the database accession number for that sequence is provided in column six. The highest scoring 'Subject' is reported in Table 2 if (a) the estimated probability that the match occurred by chance alone is less than 1.0e-07, and (b) the match was not to a known repetitive element. BLASTX returns alignments of short polypeptide segments of the Query and Subject sequences which share a high degree of similarity; these segments are known as High-Scoring Segment Pairs or HSPs. Table 2 reports the degree of similarity between the Query and the Subject for each HSP as a percent identity in Column 7. The percent identity is determined by dividing the number

of exact matches between the two aligned sequences in the HSP, dividing by the number of Query amino acids in the HSP and multiplying by 100. The polynucleotides of SEQ ID NO:X which encode the polypeptide sequence that generates an HSP are delineated by columns 8 and 9 of Table 2.

[059] The PFam database, PFam version 5.2, (Sonnhammer et al., Nucl. Acids Res., 26:320-322, (1998)) consists of a series of multiple sequence alignments; one alignment for each protein family. Each multiple sequence alignment is converted into a probability model called a Hidden Markov Model, or HMM, that represents the position-specific variation among the sequences that make up the multiple sequence alignment (see, e.g., R. Durbin et al., *Biological sequence analysis: probabilistic models of proteins and nucleic acids*, Cambridge University Press, 1998 for the theory of HMMs). The program HMMER version 1.8 (Sean Eddy, Washington University in Saint Louis) was used to compare the predicted protein sequence for each Query sequence (SEQ ID NO:Y in Table 1A) to each of the HMMs derived from PFam version 5.2. A HMM derived from PFam version 5.2 was said to be a significant match to a polypeptide of the invention if the score returned by HMMER 1.8 was greater than 0.8 times the HMMER 1.8 score obtained with the most distantly related known member of that protein family. The description of the PFam family which shares a significant match with a polypeptide of the invention is listed in column 5 of Table 2, and the database accession number of the PFam hit is provided in column 6. Column 7 provides the score returned by HMMER version 1.8 for the alignment. Columns 8 and 9 delineate the polynucleotides of SEQ ID NO:X which encode the polypeptide sequence which shows a significant match to a PFam protein family.

[060] As mentioned, columns 8 and 9 in Table 2, "NT From" and "NT To", delineate the polynucleotides of "SEQ ID NO:X" that encode a polypeptide having a significant match to the PFam/NR database as disclosed in the fifth column of Table 2. In one embodiment, the invention provides a protein comprising, or alternatively consisting of, a polypeptide encoded by the polynucleotides of SEQ ID NO:X delineated in columns 8 and 9 of Table 2. Also provided are polynucleotides encoding such proteins, and the complementary strand thereto.

[061] The nucleotide sequence SEQ ID NO:X and the translated SEQ ID NO:Y are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and

described further below. For instance, the nucleotide sequences of SEQ ID NO:X are useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in Clone ID NO:Z. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling immediate applications in chromosome mapping, linkage analysis, tissue identification and/or typing, and a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used to generate antibodies which bind specifically to these polypeptides, or fragments thereof, and/or to the polypeptides encoded by the cDNA clones identified in, for example, Table 1A.

[062] Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

[063] Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, and a predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing cDNA Clone ID NO:Z (deposited with the ATCC on October 5, 2000, and receiving ATCC designation numbers PTA 2574 and PTA 2575; deposited with the ATCC on January 5, 2001, having the depositor reference numbers TS-1, TS-2, AC-1, and AC-2; and/or as set forth, for example, in Table 1A, 6 and 7). The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. Further, techniques known in the art can be used to verify the nucleotide sequences of SEQ ID NO:X.

[064] The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable

host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

RACE Protocol For Recovery of Full-Length Genes

[065] Partial cDNA clones can be made full-length by utilizing the rapid amplification of cDNA ends (RACE) procedure described in Frohman, M.A., et al., Proc. Nat'l. Acad. Sci. USA, 85:8998-9002 (1988). A cDNA clone missing either the 5' or 3' end can be reconstructed to include the absent base pairs extending to the translational start or stop codon, respectively. In some cases, cDNAs are missing the start codon of translation. The following briefly describes a modification of this original 5' RACE procedure. Poly A⁺ or total RNA is reverse transcribed with Superscript II (Gibco/BRL) and an antisense or complementary primer specific to the cDNA sequence. The primer is removed from the reaction with a Microcon Concentrator (Amicon). The first-strand cDNA is then tailed with dATP and terminal deoxynucleotide transferase (Gibco/BRL). Thus, an anchor sequence is produced which is needed for PCR amplification. The second strand is synthesized from the dA-tail in PCR buffer, Taq DNA polymerase (Perkin-Elmer Cetus), an oligo-dT primer containing three adjacent restriction sites (XhoI, Sall and ClaI) at the 5' end and a primer containing just these restriction sites. This double-stranded cDNA is PCR amplified for 40 cycles with the same primers as well as a nested cDNA-specific antisense primer. The PCR products are size-separated on an ethidium bromide-agarose gel and the region of gel containing cDNA products the predicted size of missing protein-coding DNA is removed. cDNA is purified from the agarose with the Magic PCR Prep kit (Promega), restriction digested with XhoI or Sall, and ligated to a plasmid such as pBluescript SKII (Stratagene) at XhoI and EcoRV sites. This DNA is transformed into bacteria and the plasmid clones sequenced to identify the correct protein-coding inserts. Correct 5' ends are confirmed by comparing this sequence with the putatively identified homologue and overlap with the partial cDNA clone. Similar methods known in the art and/or commercial kits are used to amplify and recover 3' ends.

[066] Several quality-controlled kits are commercially available for purchase. Similar reagents and methods to those above are supplied in kit form from Gibco/BRL for both 5' and 3' RACE for recovery of full length genes. A second kit is available from Clontech which is a modification of a related technique, SLIC (single-stranded ligation to single-

stranded cDNA), developed by Dumas et al., Nucleic Acids Res., 19:5227-32 (1991). The major differences in procedure are that the RNA is alkaline hydrolyzed after reverse transcription and RNA ligase is used to join a restriction site-containing anchor primer to the first-strand cDNA. This obviates the necessity for the dA-tailing reaction which results in a polyT stretch that is difficult to sequence past.

- [067] An alternative to generating 5' or 3' cDNA from RNA is to use cDNA library double-stranded DNA. An asymmetric PCR-amplified antisense cDNA strand is synthesized with an antisense cDNA-specific primer and a plasmid-anchored primer. These primers are removed and a symmetric PCR reaction is performed with a nested cDNA-specific antisense primer and the plasmid-anchored primer.

RNA Ligase Protocol For Generating The 5' or 3' End Sequences To Obtain Full Length Genes

- [068] Once a gene of interest is identified, several methods are available for the identification of the 5' or 3' portions of the gene which may not be present in the original cDNA plasmid. These methods include, but are not limited to, filter probing, clone enrichment using specific probes and protocols similar and identical to 5' and 3' RACE. While the full length gene may be present in the library and can be identified by probing, a useful method for generating the 5' or 3' end is to use the existing sequence information from the original cDNA to generate the missing information. A method similar to 5' RACE is available for generating the missing 5' end of a desired full-length gene. (This method was published by Fromont-Racine et al., Nucleic Acids Res., 21(7):1683-1684 (1993)). Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcript. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest, is used to PCR amplify the 5' portion of the desired full length gene which may then be sequenced and used to generate the full length gene. This method starts with total RNA isolated from the desired source, poly A RNA may be used but is not a prerequisite for this procedure. The RNA preparation may then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA, which may interfere with the later RNA ligase step. The phosphatase, if used, is then inactivated and the RNA is treated with tobacco acid pyrophosphatase in order to

remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase. This modified RNA preparation can then be used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction can then be used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the connective tissue antigen of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the relevant connective tissue antigen.

[069] The present invention also relates to vectors or plasmids, which include such DNA sequences, as well as the use of the DNA sequences. The material deposited with the ATCC (deposited with the ATCC on October 5, 2000, and receiving ATCC designation numbers PTA 2574 and PTA 2575; deposited with the ATCC on January 5, 2001, having the depositor reference numbers TS-1, TS-2, AC-1, and AC-2; and/or as set forth, for example, in Table 1A, 6 and 7).is a mixture of cDNA clones derived from a variety of human tissue and cloned in either a plasmid vector or a phage vector, as shown, for example, in Table 7. These deposits are referred to as "the deposits" herein. The tissues from which some of the clones were derived are listed in Table 7, and the vector in which the corresponding cDNA is contained is also indicated in Table 7. The deposited material includes cDNA clones corresponding to SEQ ID NO:X described, for example, in Table 1A (Clone ID NO:Z). A clone which is isolatable from the ATCC Deposits by use of a sequence listed as SEQ ID NO:X, may include the entire coding region of a human gene or in other cases such clone may include a substantial portion of the coding region of a human gene. Furthermore, although the sequence listing may in some instances list only a portion of the DNA sequence in a clone included in the ATCC Deposits, it is well within the ability of one skilled in the art to sequence the DNA included in a clone contained in the ATCC Deposits by use of a sequence (or portion thereof) described in, for example Tables 1A or 2 by procedures hereinafter further described, and others apparent to those skilled in the art.

[070] Also provided in Table 7 is the name of the vector which contains the cDNA clone. Each vector is routinely used in the art. The following additional information is provided for convenience.

[071] Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128,256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res.* 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., *Nucleic Acids Res.* 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., *Strategies* 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene.

[072] Vectors pSport1, pCMVSPORT 1.0, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus* 15:59- (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR[®]2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).

[073] The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the deposited clone (Clone ID NO:Z). The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

2025-04-03 10:30:00

[074] Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of connective tissue associated genes corresponding to SEQ ID NO:X or the complement thereof, polypeptides encoded by SEQ ID NO:X or the complement thereof, and/or the cDNA contained in Clone ID NO:Z, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

[075] The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

[076] The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

[077] The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the connective tissue polypeptides of the present invention in methods which are well known in the art.

[078] The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or the cDNA sequence contained in Clone ID NO:Z. The present invention also provides a polypeptide

comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X or a complement thereof, a polypeptide encoded by the cDNA contained in Clone ID NO:Z, and/or the polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, a polypeptide encoded by the cDNA contained in Clone ID NO:Z and/or a polypeptide sequence encoded by a nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of, the complement of the nucleic acid sequence of SEQ ID NO:X, a nucleic acid sequence encoding a polypeptide encoded by the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the cDNA contained in Clone ID NO:Z.

[079] Moreover, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in Table 1B column 6, or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in Table 1B column 6, or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by

the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[080] Further, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1) and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1) and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1) and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[081] Further, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2), or any combination thereof.

2025-04-15 14:54:54

Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2), or any combination thereof. In further embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2) and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2) and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in column 6 of Table 1B which correspond to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2) and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (See Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[082] Moreover, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in the same row of Table 1B column 6, or any combination thereof. Additional, representative examples of polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the sequences delineated in the same row of Table 1B column 6, or any combination thereof. In preferred embodiments, the polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the complementary strand(s) of the

sequences delineated in the same row of Table 1B column 6, wherein sequentially delineated sequences in the table (i.e. corresponding to those exons located closest to each other) are directly contiguous in a 5' to 3' orientation. In further embodiments, above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1B, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1B, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated in the same row of Table 1B, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[083] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1B, column 2) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[084] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. In preferred embodiments, the delineated sequence(s) and polynucleotide sequence of SEQ ID NO:X correspond to the same Clone ID NO:Z. Polypeptides encoded by these polynucleotides,

other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[085] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more of the sequences delineated in the same row of column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. In preferred embodiments, the delineated sequence(s) and polynucleotide sequence of SEQ ID NO:X correspond to the same row of column 6 of Table 1B. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[086] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[087] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the

invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[088] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1B are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[089] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1B are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides, are also encompassed by the invention.

[090] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other

polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[091] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 corresponding to the same Clone ID NO:Z (see Table 1B, column 1) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[092] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, a polynucleotide sequence in which the 3' 10 polynucleotides of one sequence in column 6 corresponding to the same contig sequence identifier SEQ ID NO:X (see Table 1B, column 2) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[093] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 corresponding to the same row are directly contiguous. In preferred embodiments, the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B is directly contiguous with the 5' 10 polynucleotides of the next

sequential exon delineated in Table 1B, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[094] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. Accordingly, for each contig sequence (SEQ ID NO:X) listed in the third column of Table 1A, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, b is an integer of 15 to the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14. More specifically, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a and b are integers as defined in columns 4 and 5, respectively, of Table 3. In specific embodiments, the polynucleotides of the invention do not consist of at least one, two, three, four, five, ten, or more of the specific polynucleotide sequences referenced by the Genbank Accession No. as disclosed in column 6 of Table 3 (including for example, published sequence in connection with a particular BAC clone). In further embodiments, preferably excluded from the invention are the specific polynucleotide sequence(s) contained in the clones corresponding to at least one, two, three, four, five, ten, or more of the available material having the accession numbers identified in the sixth column of this Table (including for example, the actual sequence contained in an identified BAC clone). In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example. All references available through these accessions are hereby

incorporated by reference in their entirety.

TABLE 3

Clone ID NO: Z	SEQ ID NO: X	Config ID:	Range of a	EST Disclaimer Range of b	Accession #'s
HABGB54	11	952557	1 - 142	15 - 156	
HACAD23	12	926345	1 - 429	15 - 443	T26996, AW166535, AI096808, F07943, AI373466, and AI693899.
HACAI48	13	575814	1 - 187	15 - 201	
HACBA49	14	722875	1 - 414	15 - 428	
HACBT81	15	855720	1 - 342	15 - 356	
HACCY20	16	845144	1 - 342	15 - 356	
HADAM37	17	731696	1 - 392	15 - 406	
HADAM69	18	699190	1 - 451	15 - 465	
HADAR35	19	705743	1 - 446	15 - 460	
HADCK83	20	609846	1 - 668	15 - 682	AL042853, AI254913, AL138455, AI440117, AI554471, AL135357, AA769402, AA837741, AW245747, AL042753, AL037683, AA594157, AW081871, AI859946, AI253987, AA179163, AI085242, AL043289, AL043052, AA654781, AL040038, AA129746, AI249880, AA828395, AA446649, AL038606, AA768247, AW022655, AI251034, AL042538, AW023662, AI366555, AA464739, AA516190, AL040319, AW303098, AI696962, AA579419, AL042377, AA856841, AW303142, AI250552, AL035420, U89335, AC005879, AC007371, AC006115, AJ003147, AC005233, Z84484, AC005538, AC002563, AC007546, AL022336, AL021918, AC005899, AC006285, AC005940, AC005013, AL121603, AL023807, AF196779, AF207550, AC005102,

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HADCL22	21	674427	1 - 402	15 - 416	AI700450, AI939604, AI201816, AI199345, and Z94161.
HADCO14	22	657572	1 - 295	15 - 309	AC004933.
HADCO44	23	716559	1 - 320	15 - 334	
HADCO48	24	865306	1 - 387	15 - 401	
HADCO54	25	467197	1 - 355	15 - 369	
HADCO57	26	734705	1 - 317	15 - 331	AL080313.
HADCQ37	27	970564	1 - 833	15 - 847	AW007846.
HADCU18	28	666360	1 - 436	15 - 450	
HADCW65	29	719810	1 - 288	15 - 302	AI215882, AA843578, AA479185, AI274524, AA383684, AA303411, F21903, AI868651, W77995, AI433148, AI693776, AA625709, AA235619, AW151261, AA936827, AI367631, AI249488, AA861454, AA302641, AI917956,

					AA421010, AI439022, AA447665, AA554318, AW083118, AI373036, AI806892, AA156886, AI085888, AA776515, AI335769, AI446645, D59872, AI190425, AA974206, AA252189, AI142943, AI359892, AI142945, AI829611, R66420, AI590628, AW131642, AA722880, AL037830, H43132, AA779652, AI077663, AI050013, AA678939, AA594115, AI168324, AA766077, AA336082, W93317, W73178, W73952, N21569, AI015576, AW265759, AA447813, H84185, AA535245, AA410845, and C21518.
HADCX38	30	705751	1 - 426	15 - 440	
HADDB75	31	757028	1 - 463	15 - 477	
HADDC66	32	787301	1 - 473	15 - 487	AA453499, and AL049563.
HADDE78	33	773552	1 - 307	15 - 321	
HADDF89	34	786876	1 - 394	15 - 408	AW275510, AW270343, T06754, AA493695, AA635739, AI133297, AL119691, AW168618, AI473475, AA484373, AA639326, AA299189, AW023990, AW021735, AI311927, AA541423, T59524, R86151, AL038705, AA101689, AA765736, AA493708, AA745406, AI687343, AA580808, AW193461, AA572713, AL048925, AA634889, AI284640, AI751216, AI345157, AI039584, AW021207, AA829039, AA569471, AI306191, AW084466, AA469451, AI305894, AA279421, AI801482, AA806796, AA984801, AW302903, AW193265, AA526787, AL135377, AI559251, AA668807, R17793, AI350211, AA483223, AL036037, AI674174, AL037771,

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HADDQ25	35	849002	1 - 372	15 - 386	AC007406, and AL121653.
HADEU56	36	733346	1 - 461	15 - 475	AC003002.
HADFG58	37	727536	1 - 285	15 - 299	AA779075, AI371007, AA127347, AA077952, N24841, AA339714, AW057699, AI820539, AA503258, AW304531, AW407578, AI561116, AA437405, AI453383, AI254798, F12535, AI683682, AL045077, AI216799, AW238127, AW274349, AI890348, AW303196, AW301350, AI378729, AA573033, AI830390, AL037554, AL049758, AP000555, AL035464, AC006511, AC000070, AC005858, AC005040, AC002350, AC005722, AC002550, AC009464, AC005243, AC005254, AC004895, AC002553, Z99289, U60062, AL021977, AC002425, AC004494, X96421, AL035072, AL109627, Z99943, AC006040, AF141325, AP000349, AL049757, AP001037, AC002072, AC002996, AC008008, AC008045, AC005562, AC006596, AC005829, AC005756, Z84480, AL034369, AP000689, AC004448, AL020995, AC005399, AC010200, AB003151, AC010170, AC005409, AC005874, AF134471, AC006111, AC006515, AC002041, AL031255, AC006538, AC006115, Y10196, AP000066, U47924, AC000075, AC004796, AC005664, AC005280, AC004765, AC000097,

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HADFX30	38	970565	1 - 407	15 - 421	AW156911, AC005829, AL121603, AC005520, AL049793, AL049712, AL024507, AB015355, AC004491, AL022329, AL035086, AC004019, AL022326, AL035413, AL031681, Z99943, AC005057, AC005081, AC007225, AC002126, AL080317, AC006205, AL022316, AP000555, AC004821, AC009247, AL135744, AC004099, AC007308, AC005663, AC005920, AC005924, AC005914, AC002070, AC007666, AC005808, AC006487, AC007546, AC005899, AL049839, Z95331, AL022336, AL022311, AL133245, AC000052, AC005622, U85195, U80017, AC006285, AC006509, AC005037, AB003151, AE000658, AC000120, AC004966, AF165926, AC002425, AC005625, AC005531, AC004000, AC006277, L78810, AL035422, Z98941, AC007226, AL049830, AL022320, AC004814, AL050307, AL020997, AL121652, AC004382, AC006071, AC009363, AL035685, AC002477, AP000008, AC007011, U78027, AC005091, AL031685, AL109801, AL050308, AP000704, AP000501, AC004893, AC005365, and AL049760.
HADFX35	39	675830	1 - 437	15 - 451	
HADGA36	40	705766	1 - 142	15 - 156	AW004899, and AL022315.

HADGD54	41	729761	1 - 452	15 - 466	AA320586, AA847399, and Z98751.
HADGE37	42	744768	1 - 247	15 - 261	R87697, R87196, AA323557, AA324542, and AB018269.
HADGR61	43	848971	1 - 454	15 - 468	AJ223366.
HADXA61	44	741926	1 - 290	15 - 304	
HARMG09	45	705996	1 - 399	15 - 413	
HARMG60	46	933284	1 - 418	15 - 432	
HARMM43	47	714763	1 - 568	15 - 582	
HARMP39	48	705255	1 - 584	15 - 598	
HARMP42	49	713247	1 - 486	15 - 500	
HARMS39	50	933273	1 - 516	15 - 530	
HARMS77	51	752659	1 - 369	15 - 383	AC005104.
HARMU03	52	923179	1 - 178	15 - 192	
HARMX01	53	915475	1 - 795	15 - 809	AI151176, AI539290, AI539301, and AA583214.
HARMX35	54	759963	1 - 270	15 - 284	
HARNC40	55	710613	1 - 572	15 - 586	
HARND80	56	864604	1 - 610	15 - 624	AA299458, and AA704983.
HARNH15	57	687972	1 - 554	15 - 568	
HARNH52	58	726277	1 - 333	15 - 347	
HARNO29	59	690043	1 - 378	15 - 392	
HAWAD93	60	508724	1 - 327	15 - 341	AA320055, and AA320651.
HAWAP49	61	537199	1 - 402	15 - 416	AI734261, AA302758, AA320387, W21246, and AI668672.
HBIMG05	62	930827	1 - 560	15 - 574	AL118898, and AB006622.
HBIMS01	63	913827	1 - 601	15 - 615	
HBIOO63	64	969020	1 - 337	15 - 351	AA397622, T05793, AW163073, AI878983, N52689, and T05288.
HBIOP02	65	918022	1 - 98	15 - 112	

HBIO5	66	930776	1 - 457	15 - 471	
HBIOX83	67	965609	1 - 400	15 - 414	D31021, and Z98258.
HERAC86	68	973654	1 - 672	15 - 686	
HERAC92	69	973454	1 - 489	15 - 503	AW193265, AW341903, AI061334, AI688846, AA843450, AI962050, AA743811, AA657835, AI344844, AI446205, AW080134, AI803809, AI281474, AW236342, AW270768, AW419262, AI350211, AW157005, AI028510, AW438643, AL039187, AA992126, AW151102, AA745356, AI284640, AA904275, AI014378, AI963720, AW029038, F17700, AW167154, AA515051, AI053672, H57846, H79308, AA747375, AA669961, AI580652, AA350859, AA352290, AW193432, AW265688, AI569086, AW008074, AI801600, AI082510, AI633007, AW275719, AA744272, T48723, AI583142, AA744001, AA745524, AI291037, AI251002, AW408063, F18974, AI270326, AW102955, AI283938, AA482711, AA074130, AW277174, AI291124, F31204, AW088058, F02412, AA491814, AW265294, AA865262, AW104748, AI679782, AI929531, AI610920, H62778, T05834, AI345654, AA744455, AI185394, AA557879, AI446464, AI431303, AA365586, AL041368, AA832016, AI291268, AA955031, AA526193, AA831801, AA493238, AI049722, AI282832, AA826303, F33566, AA228778, AA229785, AA358623, F37286, AI291823, AI537030, AL120483, AI918421, AA745588, AI339850, F28576, AA311535, AI341664, AA743966,

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HERAD04	70	927788	1 - 316	15 - 330	
HERAD10	71	973489	1 - 361	15 - 375	
HERAD21	72	954708	1 - 311	15 - 325	AI638717.
HERAG57	73	973668	1 - 277	15 - 291	
HERAJ78	74	973676	1 - 652	15 - 666	AI809453, and AL031682.
HERAL93	75	974497	1 - 522	15 - 536	
HERAM84	76	529193	1 - 249	15 - 263	Z55723, and Z65235.
HERAN13	77	973709	1 - 642	15 - 656	
HERAR12	78	735275	1 - 375	15 - 389	AI927443, AI266358, AA132549, AI079981, AI870712, AW263428, AA490266, AW418652,

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HESAD92	79	537451	1 - 388	15 - 402	AC005218.
HESAT22	80	537449	1 - 340	15 - 354	
HESAT88	81	537446	1 - 210	15 - 224	
HFEAG37	82	705454	1 - 221	15 - 235	AA339935, and Z99289.
HFEAH35	83	504585	1 - 285	15 - 299	AA339994, AA340086, and AL132987.
HFEAN02	84	932828	1 - 207	15 - 221	AA339972.
HFEAN43	85	524355	1 - 302	15 - 316	AI814735, AW193432, AW276435, AA654968, AI688846, AA649642, AW301350, AW303196, AW274349, T07451, AW193265, AW261871, AA350859, AI619997, AA515128, AW088058, AW088202, AI350211, AW302450, AA594145, AL041690, AI929531, AI962050, AW029038, AI471481, AA225155, F18974, AI061334, AA664407, AW419262, AI270117, F31204, AW438643, AI625244, AI499938, AI061296, AI564185, AI339850, AI469003, AA557879, AW236342, AA515051, AW264973,

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HFEAO67	86	954402	1 - 332	15 - 346	AA339975, and D79987.
HFEAQ11	87	530368	1 - 228	15 - 242	L05187.
HFEAS89	88	960624	1 - 297	15 - 311	
HFEBB19	89	974533	1 - 315	15 - 329	
HFEBB35	90	974535	1 - 344	15 - 358	AC004832.
HFEBD62	91	789763	1 - 384	15 - 398	R83124, and AA196223.
HFEBF21	92	974270	1 - 677	15 - 691	
HFEBG06	93	935683	1 - 400	15 - 414	
HFEBL88	94	766085	1 - 347	15 - 361	
HFJAA51	95	725626	1 - 38	15 - 52	
HFJAA62	96	855107	1 - 317	15 - 331	
HKAAU11	97	966953	1 - 500	15 - 514	
HKABE64	98	879492	1 - 498	15 - 512	AW376201, and AA627838.
HKABR48	99	702372	1 - 809	15 - 823	AA425985, AW207504, and AI814319.
HKACB30	100	466848	1 - 457	15 - 471	AI458016, R21817, AI868552, and R31545.
HKACG80	101	750256	1 - 260	15 - 274	AW090350.
HKACL95	102	973360	1 - 438	15 - 452	AL050402.
HKACM63	103	952653	1 - 340	15 - 354	
HKACU93	104	908022	1 - 680	15 - 694	AI638185, AI671593, R71971, T50004, AL046617, AI914383, AW138307, AI674324, AI949564, AI142072, AA570066, AI742499, AI479463, T50068, AI122805, AI761880,

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HKACY54	105	862787	1 - 344	15 - 358	AI292099, H18280, AA485264, W38023, AA007261, AW136965, AW269962, W78976, AI904882, W80358, and AA514672.
HKADC82	106	944994	1 - 517	15 - 531	AA256009, and Z73417.
HKADP74	107	765535	1 - 582	15 - 596	W94875, AL041446, AW246310, AF063308, and AC005726.
HKAE04	108	857355	1 - 342	15 - 356	AI125876.
HKAE60	109	812691	1 - 282	15 - 296	AI910382, AI219334, AI219219, AI760454, AI738963, AA339789, C00167, and AL031848.
HKAEP23	110	672808	1 - 452	15 - 466	AW247811, AW250381, and AA380312.
HKAEP94	111	973353	1 - 338	15 - 352	AC008039.
HKAEP36	112	930711	1 - 377	15 - 391	AI128862, AI436219, AI762629, AI140124, AI083708, AI560407, N99923, AI081307, AI079414, AW075617, AI818253, AI337194, AI051901, AA977275, AW172809, AA844432, AI028509, N90737, AI129280, AI305175, AI093068, AA917896, AI371771, N33210, AI969645, AW274900, AA767460, AI968452, N62347, AI220982, AI366857, AI339129, AI767826, N22977, AI468435, AA808772,

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HKAFO42	113	713722	1 - 542	15 - 556	R94601, AA342675, AW131267, F02125, AA236551, R81911, AI678532, H15432, AA599318, AA620448, AA535635, AI394475, R38735, T67404, T68558, R73365, T68316, T85192, AL043229, R70120, U96629, AC004765, AL049553, AP000348, AF088219, AC007685, AL031291, AL049830, AC004491, AC005231, AC005531, D87675, AF126403, AC005753, AC005399, AC005015, AC006285, Z95113, AC007055, AL096701, AC005529, AC005527, AL109963, AC006141, AC004675, AC005519, Z98941, AC004750, AC004854, AC004477, AC006449, AL034417, AC004596, AF024533, AC000353, AL109952, Z85987, AC005233, AC006512, AC005666, AC007541, AL049832, AC002472, AC007227, AC004647, AC002483, AC006487, M89651, AC004079, AC005088, AC004583, AL079295, AC003029,

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HKAFZ12	114	970570	1 - 463	15 - 477	
HKAHF84	115	887386	1 - 320	15 - 334	AF095719.
HKAHI83	116	780669	1 - 504	15 - 518	AC005598.
HKAHT29	117	958404	1 - 45	15 - 59	
HKAIF25	118	974416	1 - 213	15 - 227	
HKAIL12	119	893937	1 - 287	15 - 301	AL035588.
HKAU82	120	779322	1 - 502	15 - 516	
HKAJG02	121	857330	1 - 660	15 - 674	AI609622, AI668709, AA747150, and N93967.
HKAJR01	122	915313	1 - 267	15 - 281	
HKAJW52	123	836587	1 - 158	15 - 172	AF154107, and AJ245539.
HKAKI80	124	973231	1 - 560	15 - 574	AC004991.
HKAKL94	125	782287	1 - 106	15 - 120	AI239832, and N36064.
HKAKP85	126	927032	1 - 361	15 - 375	
HKAOE10	127	963543	1 - 512	15 - 526	AI969269, R39098, AA811689, AA302657, W27874, AA308708, R94832, AA767864, R84431, AI374601, Z96210, Z96209, AC009225, AC005015, AL109782, AC002472, AC002070, AC002470, AL022476, AL078583, AB004907, AC006930, AC004686, AL009172, AC004462, AC004461, L77570, AC005514, AL078621, AC005874, AF134471, AC005815, AC002395, AC005920, AC005187, AL121658,

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HKAOM71	128	761303	1 - 479	15 - 493	
HKAON82	129	779247	1 - 583	15 - 597	AA284297, W46190, AI301143, W46354, AA258492, AW183753, AI864177, AF086184, and AF093239.
HKAOU93	130	791779	1 - 742	15 - 756	AW451488, AI338940, R62633, W72910, AI739528, AI016891, AI147482, R78135, H87957, and R63510.
HKAPN78	131	973220	1 - 809	15 - 823	AW083934, AA809546, AA128511, AA601376, AL119483, AA640305, H73230, AI053911, AA826079, AA730530, AA572715, AI040051, H58354, AI242994, AW419389, AA302973, T50694, AA470933, AA862243, AA832077, AI682665, AI753488, C14614, AA574442, AI620014, AI567676, AI619933, AA603530, AA483599, AA483912, AI570067, H61079, AA380695, AL109627, AC004460, AL023553, AC004760, AF165926, AL121603, AC003109, AL049830, AC004167, AC000004, AC004491, AL031230, AP000555, AL049776, AC005520, AL022313, AL049793, AC003030, AF001549, AI031846, AC004253, Z97056, AC006312, AC004975, AC004150, AF196779, AL022721, AC005786, Z84486, AP000692, AC005253, AC005777, AC005393, AC008044, AC004125, AL021408, AP000245, AC007565, AC006211,

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HOUDC46	139	719181	1 - 413	15 - 427	
HOUDJ40	140	573873	1 - 393	15 - 407	
HOUDN50	141	724607	1 - 59	15 - 73	
HOUDX25	142	524248	1 - 308	15 - 322	AI547239, and AR040737.
HOUEN50	143	573874	1 - 271	15 - 285	AC010517, and M20439.
HOUFB87	144	837251	1 - 1273	15 - 1287	T07874, AA410788, AA228778, AW069227, AA721645, AA284247, AA176604, AI056177, AA862183, R16221, AA984263, AW403644, AI457313, AI446336, AI634187, R81017, AA176978, AA916430, AI282479, AI251429, AI678867, W02749, AW084445, AA757426, AI571161, AA527209, AA713705, AI791185, AA668455, AI049504, AW192373, AI744905, AI362442, AI890324, AI821076, AA371519, Z82190, AL031255, AL022326, AC016830, Y14768, AP000505, AC005049, AC002316, AC008115, AL049760, AC016027, AP000350, AC006430, AL008729, AC002310, AC003663,

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HOUFQ33	145	701762	1 - 233	15 - 247	AC007566.
HOUFT79	146	774089	1 - 247	15 - 261	
HOUFV24	147	676834	1 - 465	15 - 479	
HOUFV31	148	697592	1 - 507	15 - 521	

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HSTAL08	159	960473	1 - 345	15 - 359	AA379434, AA379435, AA380002, and AA380033.
HSTAL23	160	508812	1 - 295	15 - 309	AL134728, AA379440, AA379975, and AC008064.
HSTAL64	161	508813	1 - 322	15 - 336	AA379527, AI758948, AA379948, and AA379262..
HSTAL92	162	508820	1 - 288	15 - 302	AA379412, AA379324, and AL023694.
HSTAO16	163	508808	1 - 346	15 - 360	AA379691, AA379508, and AA199864.
HSTAP23	164	508802	1 - 334	15 - 348	AA379825, and AA379564.
HSTAP31	165	508803	1 - 277	15 - 291	AA379769, AA379768, and AA379568.
HSTAP89	166	508805	1 - 310	15 - 324	AA379549, AA379695, and AA379479.
HSTAQ54	167	968671	1 - 280	15 - 294	AA379987, AA379631, AA379302, and AA379303.
HSTAQ67	168	508800	1 - 401	15 - 415	AA379713, AA379585, and AI909060.
HSTAX16	169	508960	1 - 98	15 - 112	AA379755, and AA379612.
HSTAX68	170	508797	1 - 122	15 - 136	AA379715, and AA379716.
HSTAZ54	171	508368	1 - 323	15 - 337	AA379890, AA379972, AB011162, and AL133297.
HSTBC04	172	506961	1 - 276	15 - 290	T35873, T35870, AA379980, R09424, M79174, R16269, AA286926, AW387005, AA115072, AW387011, AA480967, AW386994, AA160074, AA419194, AA573369, AL050149, Y08698, Y08697, AC004602, and Y08699.

HSTBJ41	173	526608	1 - 197	15 - 211	AA380153, AA380233, and Z83851.
HWDAC04	174	927471	1 - 388	15 - 402	W95816.
HWDAC71	175	752776	1 - 122	15 - 136	
HWDAG13	176	746132	1 - 354	15 - 368	
HWDAN69	177	676671	1 - 574	15 - 588	
HWDAO04	178	927231	1 - 316	15 - 330	AI298104.
HWDAO26	179	679520	1 - 436	15 - 450	AP000127, AP000205, AP000244, and U03686.
HWDAP03	180	923319	1 - 360	15 - 374	AI524995, AL078621, and Z96200.
HWDAS34	181	703610	1 - 413	15 - 427	AI734130, AI732734, AI741241, AA433997, AW043563, AI732741, AA437369, AA425820, AA426284, AL133619, AC004033, and AC007050.
HWDAS64	182	729159	1 - 480	15 - 494	
HWDAS93	183	707809	1 - 202	15 - 216	
HWEAD11	184	965030	1 - 419	15 - 433	AA316239, and AA015579.
HWHGB20	185	669455	1 - 695	15 - 709	AW062329, W70164, AA706790, AA328482, AA328483, AI818367, AI858617, AA007658, AI697948, AI571759, AI096775, W07379, AA007657, AA733044, AI363365, AI123638, AI126856, AW015811, AA946988, AI571898, AI962208, AI365427, AI651148, AI970105, N80253, AI079735, AI983461, AW136943, AA040945, AW339376, W70106, AA983291, and AF037222.
HWHGB21	186	954002	1 - 514	15 - 528	
HWHGB32	187	698891	1 - 402	15 - 416	AA465324, AI541453, H93411, AA837473, D56451, AW008969, AI797289, D56220, AI394269, N30347, Z36872, H63216, AA248589, and AW009897.
HWHGB44	188	716369	1 - 401	15 - 415	

HWHGL42	189	908227	1 - 432	15 - 446	N57568, and T16687.
HWHGW34	190	670622	1 - 422	15 - 436	
HWHHA18	191	665788	1 - 466	15 - 480	
HWHID04	192	926251	1 - 487	15 - 501	AA429236, and AA436572.
HWHJA12	193	969044	1 - 580	15 - 594	AW449534, AI421055, and AA463364.
HWHPF38	194	709502	1 - 390	15 - 404	W86770, AA248713, and AC005042.
HWHPF60	195	675703	1 - 843	15 - 857	W79014, T56655, H73294, R08414, N77361, W80406, AW364174, AI078359, AI051883, AA783039, AA476762, N74662, AF086122, and U91318.
HWHPJ63	196	744720	1 - 364	15 - 378	
HWHPT41	197	658138	1 - 457	15 - 471	
HWHQA86	198	785281	1 - 421	15 - 435	AC005034.
HWHQI82	199	739230	1 - 203	15 - 217	AA625249, AA402169, AC007059, and AC006128.
HWHQO07	200	952660	1 - 297	15 - 311	R33091, AC004884, AC007938, AC003982, AF111168, AC006376, and AC005046.
HWHQO33	201	670190	1 - 323	15 - 337	AA463659, AC007455, and D86424.
HWHQP22	202	674151	1 - 331	15 - 345	AI688658, AI341299, AI208033, AI807003, AI653327, AA812828, and AW451464.
HWHQV08	203	958709	1 - 424	15 - 438	
HWHQV13	204	656647	1 - 413	15 - 427	AA430137, AW179305, AW179306, AA828637, AW168383, T62539, AA483126, AL049832, AL008582, AC007790, AC000134, AC004452, AC005553, AC007773, AL121653, AL121658, AB028964, AL049694, AC004644, AP000355, AC002051, U73629, AC002054, AC010168, AP000550, AC009275, AC007664, AF165926, AC008018, AC005013, AC004228, AC004594, AC000028, AL109984, AL035587,

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HWHQV57	205	734455	1 - 552	15 - 566	AC005005.
HWHQX34	206	703785	1 - 377	15 - 391	
HWHQX77	207	771865	1 - 375	15 - 389	AA053463, AI431513, AA633799, H68343, H53546, AA302978, AI445373, T52366, AI003988, AA678932, AW440568, AA679625, AI798521, AA568971, AW238341, AI915081, AA744094, AA599080, T49451, AI445338, AA846923, AI302350, AW270258, AA573062, AA587826, AL042667, AL042670, AI049504, AA768179, T03576, AI433952, AI590404, T41134, AI049701, AA484298, AW081610, AW407974, AA526643, AA482323, AI619994, AA551548, N72678, AA632556, N73540, AI066646, AI357628, D58782, AI955029, AI300818, AA714140, T47739, AA584360, AA574286, AA373861, AA654038, AI499941, AI889579, AW238016, AL137946, AA633875, AL119563, AA515168, AA194858, AA323085, AI307563, AW152439, AI216981, AA018923, AI524022, R93882, AI738863, AA744048, AI224619, AI039257, AI310992, AA515351, AA514450, AI978712, AA507637, AW173443, AA533660, AI446574, AA513884, AL036665, AI869797, AA657374, AA478602, AL049776, AC006088, AC002470, AC006160, AP000965, AF134726, AE000661, AF107885, AC005358, AC005666, AC004983, AL031387, AC008009,

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HWHQY18	209	628987	1 - 540	15 - 554	AI961281, W25575, W73855, AA025948, W69100, W95776, W92535, W69380, AA359882, W68286, AA46828, AA022503, AI131566, AA706316, AA777022, AA480817, W95987, C00662, W95733, AI161236, AI141167, AW001367, W58747, AI148339, AA854719, AW009909, W94659, AI092860, AI150077, AI144221, AW009219, AD001502, and AF086315.
HWHQY36	210	708384	1 - 398	15 - 412	AA046311, AI083557, AI206370, and C00645.
HWHRA44	211	716334	1 - 297	15 - 311	AI168274, AI284425, AI950359, AI801031, AA461430, AW191939, AA573663, W80696, M77904, AA618172, AA468952, AA632469, AA534221, AA632695, AA774006, AI249128, T68597, AA210711, AA174138, AI251576, AI306232, AW274191, AA985662, AI583466, AA468491, AI734154, AI473995, AI732760, AI073373, T49184, W24698, AI283022, AA385740, AA318347, AI891038, AI092694, AA491864, AA579437, AI285486, AA501781, H73306, N53352, H27102, N21111, AI754286, W45073, AI204350, AI114828, H05449, AA705418, AA665248, AA481408, AI678676, F31203, AI002969, AA906657, AA632493, AA632484, AI274006, AA736485, AA805014, AI382205, AI567831, W38349, AA480216, AA501976, AA366601, AI445768, AW419389, AA586553, T96546, AA525963, AA568314, AI889648, AI613487, AA653009, H58891, AI336206, AA326245, AA742775, AI298166,

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HWHRA91	212	789529	1 - 360	15 - 374	AA209277, L44490, AC002504, and D49678.
HWJAC59	213	761620	1 - 95	15 - 109	AW168031, AW105429, AI669639, AA508657, AW074702, AI677797, AI524179, AI631398, AI886206, AI089970, AW085786, AI824648, AW189802, AL040011, AW151034, AI745713, AA514684, AI567827, AI597918, AI887163,

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HWJAC71	214	760084	1 - 305	15 - 319	
HWJAD16	215	661520	1 - 341	15 - 355	R93869, AI682502, AA211116, C14990, AI217197, C15248, AA633619, and AA405558.
HWHQW24	216	907997	1 - 666	15 - 680	R85195, AA443410, AA401263, AA037299, H43770, R87693, H51243, N42852, N29204, R88559, H30680, N34077, U47344, R87576,

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HWHQS58	217	869780	1 - 830	15 - 844	AA129755, AI264327, AI924548, AW373421, AW044471, AW373417, AI591124, AA521147, AI431599, AA521164, AI275624, AI245547, AI684030, AI916377, AI493958, AI685167, AI160092, AA133232, D25665, AI423062, AA449480, AI040218, AA232960, N94960, AA062910, AA748581, N78938, AA255901, AA814767, AA521125, AA243720, AI358080, AA838769, AI973219, T86115, AA834077, AA861136, AI025566, AI202152, N91600, AI093292, AW014070, AI417825, AW087763, AA884806, AA468604, AA128760, AA135673, T36186, AA426039, AL044788, AA707773, AA991552, AI382484, AW381891, AA436115, R16132, AB002389, AR069019, and AR069018.
HWHQQ73	218	761719	1 - 670	15 - 684	T99288, R09823, T78999, and N74755.
HWHQO89	219	786155	1 - 481	15 - 495	W49670, R68198, R37555, and AL122007.
HWHQL42	220	805897	1 - 440	15 - 454	AI961430, AA568549, N53238, AI924984, AI149157, AA811355, AW073372, AI610339, AI758882, AI819475, AW338889, AA764930, AW189496, AI342866, AI244150, AA425635, AA976965, AI924962, AA703348, AA442907, AA469084, AW410367, AA303216, AW410368, H47257, AA084522, N64595,

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HWHL26	221	694021	1 - 588	15 - 602	AA136968, and AI380268.
HWHL31	222	697599	1 - 777	15 - 791	R56163, H04894, H11894, AI298239, and AI457203.
HWHL16	223	661553	1 - 388	15 - 402	R28114, N83626, and AF157623.
HWHL35	224	707826	1 - 433	15 - 447	W89066, T95526, AI356054, and AC004918.
HWHLB79	225	774685	1 - 592	15 - 606	H95485, H51648, AI424831, AI688141, AW341521, AI377709, AA971261, AW117535, and AC004381.
HWHPY78	226	781689	1 - 692	15 - 706	T79721, T80919, T81157, W44656, AI431747, H27541, and AI668612.
HWHPR89	227	598535	1 - 334	15 - 348	W35214, W23624, AI591033, AA436232, and AA436233.
HWHP068	228	752782	1 - 710	15 - 724	AA429919, AA430055, AA160879, AI675394, AW368947, AW379520, AB026833, AF043977, and AF127980.
HWHPM27	229	682719	1 - 384	15 - 398	AA649069, H47757, N77332, and N76749.
HWHL01	230	915610	1 - 506	15 - 520	AA010677, AA010884, AA243840, AA243576, and AC006070.
HWHPK76	231	769791	1 - 151	15 - 165	AA044915.
HWHPK51	232	725456	1 - 404	15 - 418	R82128, AB003151, and AP000688.

HWHPJ26	233	681217	1 - 307	15 - 321	N29484, and N42313.
HWHPF78	234	773407	1 - 649	15 - 663	AA761327, T08371, R16012, R16112, AA761312, and AB032976.
HWHPD16	235	661660	1 - 725	15 - 739	N25530, H98835, AI693538, AI220466, AI263186, and AI910983.
HWHPC04	236	614960	1 - 562	15 - 576	AA034067, AA703147, AA693566, AA112403, AA694480, and Z99716.
HWHPA61	237	741642	1 - 496	15 - 510	N40407, AF006752, and AC005072.
HWHKJ11	238	965201	1 - 404	15 - 418	AA630904.
HWHKG03	239	971735	1 - 1009	15 - 1023	AI573144, AI289200, AI244184, AA806849, AI193797, F08271, AA587758, AW068762, AA125767, AW379978, M63005, M63544, and M63480.
HWHJM08	240	955683	1 - 884	15 - 898	AA021558, R79554, W311198, R79555, AA972575, H41096, AA724112, F12234, R73753, R65612, AA878715, H15618, M78502, R66995, and T66395.
HWHJJ11	241	965189	1 - 371	15 - 385	AA448728, AA442797, AW090790, AP000339, and AP000217.
HWHHW50	242	724078	1 - 158	15 - 172	AA255452.
HWHHU57	243	734458	1 - 746	15 - 760	AA478923, AA195103, N77780, and AA478803.
HWHHQ10	244	963959	1 - 424	15 - 438	AA837647.
HWHHO76	245	769848	1 - 984	15 - 998	N76171, AI291047, and N64762.
HWHL02	246	919202	1 - 704	15 - 718	AA478607.
WHHGZ86	247	970662	1 - 919	15 - 933	AA775083, W28290, AW206265, and AA504965.
WHHGY82	248	779020	1 - 439	15 - 453	R01825.
WHHGY56	249	733124	1 - 396	15 - 410	H11686, H11889, M79139, AA340707, AL080149, Z98885, and AF005067.

HWHG72	250	945692	1 - 927	15 - 941	AL119324, U46341, AF190825, AF190823, AF190822, AF109387, AF109388, AF190826, AF190824, AF053328, AF053327, AF053329, U14414, Y10473, AF064549, AF020756, and AB026436.
HWHGS51	251	725446	1 - 646	15 - 660	H06904, and AA251730.
HWHGP95	252	795148	1 - 722	15 - 736	AW295449, R00307, AI247760, T99960, R00555, R00661, and AC004841.
HWHGF95	253	947019	1 - 910	15 - 924	AF135026.
HWHGE01	254	915933	1 - 642	15 - 656	W63622, T84232, and AL122023.
HWHGC93	255	915311	1 - 569	15 - 583	H42716, AW275818, AA627916, W68815, W68529, AW275825, AI969511, H25944, H25979, AI800001, and AL035408.
HWHGC57	256	942388	1 - 698	15 - 712	AW392670, U46350, U46347, AL119319, AL042542, AL119457, AW363220, AW384394, U46351, AL119324, AL119399, AL119522, AL119484, AL119391, AL119496, AL119443, AW372827, AL042544, U46349, Z99396, AL119418, AL119439, AL119363, AL119444, AL119497, AL119355, AL119483, AL119401, AL134527, AL119396, U46346, U46341, AL119341, AL119335, AL042551, AB026436, AR054110, AR066494, AR060234, and A81671.
HWHGB85	257	889955	1 - 605	15 - 619	AA494374, AA992165, AA628613, AA291410, AW161252, D61624, AA340594, AA293684, AW405954, D80282, AI816346, D59735, D60593, AA420752, AW368326, N42417, R81395, AI147058, AA456178, H18287, H23632, H29998, AA809547, H44100, R77573,

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HWHGB13	258	656712	1 - 532	15 - 546	AC007126.
HWFBH55	259	732549	1 - 457	15 - 471	AA237022, and AA302431.
HWFBG80	260	561208	1 - 432	15 - 446	AA302696, Y12853, and Z98941.
HWFBD96	261	796070	1 - 387	15 - 401	AA302745, AW341057, AA302744, T94439, AF134726, and AP000503.
HWFBFB09	262	575533	1 - 306	15 - 320	AA302794, H93962, AA302795, AA404526, AA837450, R44042, AA504562, F04351,

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HWFAD94	263	504477	1 - 503	15 - 517	AA302757, and AA302810.
HWFAD84	264	504489	1 - 629	15 - 643	AA302767, AA302766, AP000049, AP000116, and AP000311.
HWFAD65	265	753943	1 - 391	15 - 405	AI095489, AI185693, AA947166, AA302673, and AA429776.

HWEAE94	266	794026	1 - 413	15 - 427	AA160846, and AF041004.
HWEAD10	267	927208	1 - 314	15 - 328	AI310965, AI161301, AA662057, AI362584, AI287497, AI358460, AI253259, AI767640, AI276135, AA206625, AI088803, AW150301, AI805044, AW088682, AI459338, AI360735, AI139259, AW271545, AI140303, AI627186, AI868008, AI356036, AI632014, T16033, T33318, AI700386, AI671718, AA603054, AW003777, AI865463, AI955034, W93511, AI703155, AI471245, AW026798, R36872, AA552905, AA649777, AA976729, AA613313, F31652, AI703185, AW298187, AW244163, C15626, W93510, AW089275, AI002285, AI633125, AA502794, AW152182, AI886415, AI815232, AI696626, AI590423, AI537837, AW103878, AI886055, AI610671, AI564723, AI582932, AI872423, AW051088, AI698391, AI915291, AI799183, AI889189, AI473208, AI868204, W74529, AA848053, AI521560, AI553645, AW238688, AI624304, AI633061, AI621209, AI205869, AI583578, AI889376, AW029186, N33175, AI589261, AI819545, AI702073, AI383804, AI690946, AI927233, AI916419, AI623941, AI433157, AI824576, AI866461, AI925164, AI491842, AI360195, AI919534, AI865906, AW150511, AI742728, AI889882, AW084447, AW104724, AI886206, AI690472, AI440294, AI537809, AI370623, AI683979, AL045500, AW083175, AW089932, AI469573, AW148536, AA833760, AI613038,

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HWDAY07	268	952441	1 - 1271	15 - 1285	AA749085, AA005363, AW301099,

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HWDAS21	269	670233	1 - 504	15 - 518	W30898.
HWDAP89	270	795713	1 - 376	15 - 390	AI474053, W56513, AI432332, W56794, Z39374, AI147106, AI446000, AA953896, AA938917, AA431701, and AB023226.
HWD AO90	271	788546	1 - 405	15 - 419	N62679.
HWD AO63	272	744591	1 - 367	15 - 381	R09053, AA554481, AA203281, AI623801, AI799476, AI832581, AA911363, AI673515, AI016523, AA838021, AI247258, and AA682711.
HWDAL32	273	698628	1 - 556	15 - 570	H28004, AI022925, AI091318, AW275201, R50740, AI217623, AA992501, and H27302.

HWDAD75	274	973099	1 - 508	15 - 522	AW392670, AL119439, AL119484, AL134530, AL134519, U46347, AL119391, AL134528, AL042544, AL119522, AW372827, AL134525, AL119444, AL119401, AI142137, AL134524, AL119363, AL134518, AI142132, AL037205, AL042614, AL043019, AL119396, U46346, AR066494, and AR060234.
HWDAD72	275	766077	1 - 645	15 - 659	AA009796.
HWDAD54	276	729262	1 - 418	15 - 432	N68637.
HWDAD40	277	881233	1 - 433	15 - 447	AA652394, AA843652, C75018, AA669261, W87450, W87549, AA777348, AI193964, AI376931, AI955233, AA975047, AI183977, AI963358, AA970316, AI203652, AI803310, AI283867, AA587214, AW418911, AI123535, AI818338, AI370130, AA767720, F09040, AI079190, AI826448, AA102631, W42602, AW300767, W42575, AW451886, AI432609, N63983, AI686051, N79598, AI049811, AI074845, AI420650, AA121360, AA748200, AA633869, AA625311, AI817306, AI128886, R77612, W72190, AI801873, AA813658, AI216889, AI480050, H79301, AI937759, AI290367, AI351991, T55328, AI123507, Z41647, AW452908, AA918249, AI270005, W77826, AA349329, AW163174, W19065, AA357509, and AA331284.
HWDAC55	278	731414	1 - 647	15 - 661	R13600.
HSTAO59	279	908993	1 - 430	15 - 444	AA447205, AI829089, AI863429, AI922955, AW166933, AA226755, AI493118, AW139935, AI288648, AI379442, AA379460, AA442080,

					AI472968, AI204221, AW363135, AA781855, AA455072, AI637856, AW058023, AW139348, AI085392, AI393154, AI568689, AA134758, and AL109984.
HSTAH84	280	783227	1 - 759	15 - 773	AA379147, and AI362444.
HSTAG60	281	578487	1 - 314	15 - 328	AA379328, AC003025, AF139813, and AC004228.
HOUF71	282	759929	1 - 395	15 - 409	T96856, and T85931.
HOUGC71	283	760110	1 - 396	15 - 410	T98003, and AA777394.
HOUFM73	284	764173	1 - 611	15 - 625	AA053845.
HOUFM67	285	751325	1 - 120	15 - 134	
HOUFM50	286	724038	1 - 298	15 - 312	N86502.
HOUFM32	287	698816	1 - 329	15 - 343	
HOUFD93	288	791584	1 - 649	15 - 663	AA180087, and AA169293.
HOUFD09	289	625245	1 - 497	15 - 511	AI674479, AI376362, AI628358, AW207400, AW170497, AI089668, AI570878, AA777998, AI471795, AI830803, AI869793, W42429, AW237793, AW015529, AA836860, AI474249, AI203312, and AI955073.
HOUFC52	290	726438	1 - 273	15 - 287	N45644, and AF156857.
HOUET93	291	792495	1 - 353	15 - 367	H93543, AA001725, and AL022069.
HOUES18	292	577112	1 - 394	15 - 408	AI399883, AI038052, R01245, AA703404, AA865857, AI078069, R06676, and AC011331.
HOUER77	293	772417	1 - 556	15 - 570	AA082667.
HOUEM24	294	677416	1 - 440	15 - 454	AA210722, and AI872356.
HOUKE01	295	965449	1 - 552	15 - 566	T78627, AI074759, N72587, AA040182, AA987525, AI880532, AI601259, T67791, N34190, AA393320, AI089984, AA180860, N46781, AW157052, AA374237, R99057, AA180963, N25803, AA658952, AA398674,

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HOUH51	296	725820	1 - 657	15 - 671	AI377999, H97074, N46131, and AW027236.
HOUH85	297	883933	1 - 374	15 - 388	AA256607, AA256608, AI804218, AI924547, and AI452529.
HOUH29	298	576473	1 - 163	15 - 177	AA316905, AA365694, AA641175, AA523242, AI278997, AA856969, AA649722, AA503600, AA908422, AA661921, T34775, AI732378, T06828, AA688036, AA714453, AI243584, T40417, D52587, F16274, AW088984, D25870, AA135842, F34498, AA480772, R93145, AA580808, AA501821, H50727, AA525824, AA649484, W79504, AA654771, AA828749, AI364809, AA649542, AI087042, AW080134, F23335, N92703, AI540161, N27763, F19012,

H86305, AI446464, AA302648, AA729721, C17734, AI273185, F25867, AI246119, AL044940, AI291124, R97934, AA513972, F18485, AA908468, AA513293, AW265385, AA678436, AI610159, AA362349, AI291268, AI357288, F04987, AA535406, AA603156, AA934680, F15732, AA670468, AA350859, F16017, AA773902, AA056439, AI537955, AI270117, AI284640, AW270382, T05101, AA649642, AF150152, AA358410, T40077, AA669251, AI251002, AA338892, AI653905, AI434695, AA347368, AA346458, AA493206, AA658362, T07451, AA491814, R40056, AA568616, AA719080, F28737, AI298710, AA523838, AA181773, AA381858, AA225149, AI754955, F17891, AA468131, AI281697, AA534010, N94233, AA558015, AW274349, AA501578, AI372413, AA516226, AL036037, AA548058, AA634889, AA296997, D51681, AW103981, AA074130, F33795, AA551503, AA837084, AI688846, AI358571, AA352803, AI364020, AA281461, AA771811, AA331965, AA578481, AA649705, AI798489, AW089322, AA548689, AW438643, R77905, AA593247, AA634146, F17802, AA515905, AI678316, AA810370, F18320, AA369597, N87420, AI364026, AA568778, AA317190, AA478339, AI281881, AA364429, AI679045, AA826671, AA773318, AI291588, AI871722, AW276435, AW071196, N25296, AW023389, AI471481,				
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HOUDL40	299	710868	1 - 590	15 - 604	
HOUZ30	300	573930	1 - 295	15 - 309	
HOUZ25	301	559993	1 - 432	15 - 446	AI744546, AA860302, R12381, AA569600, AC005828, AC004967, AC010206, Z98950, AP000493, and AC005013.
HOUBO69	302	757808	1 - 348	15 - 362	AA889574, AA127237, AA912157, and AL035702.
HOUBD18	303	858911	1 - 374	15 - 388	AA776185, and AC002112.
HOUBB11	304	965041	1 - 415	15 - 429	AA745602, AA490944, and AA814239.
HOUAV68	305	753628	1 - 150	15 - 164	N76301.
HOUAF65	306	526540	1 - 176	15 - 190	AL038971, H47145, R11751, AA582463, AI564496, AA442105, AA812141, AA324585, AA737309, H82316, AL048925, T07044, AA455483, AI002720, AA259247, H09071, W67839, Z78390, AA402129, AL041444, R64559, AL109981, AL023281, AC007878, AC007371, AP000470, AP000689, AC009946, AC006077, AC005778, AC005002, AL031985, AC010170, AC005924, AB023049, AL121578,

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HLSAC73	307	761684	1 - 212	15 - 226		
HLSAC61	308	689697	1 - 203	15 - 217		
HLSAB43	309	715242	1 - 349	15 - 363		
HLSAB31	310	422131	1 - 356	15 - 370		
HLIBE40	311	887417	1 - 534	15 - 548		AA005293, and AA098865.
HKAQ73	312	761763	1 - 365	15 - 379		R88969, H30247, AL020995, and Z65427.
HKAOO90	313	934020	1 - 617	15 - 631		N73164, AA284448, W89194, AA446792, AA810520, AW195917, AI675774, R29088, AW172479, R26007, and AA913564.
HKAOF21	314	857310	1 - 501	15 - 515		F11238, and AC005067.
HKAKY03	315	923047	1 - 334	15 - 348		N94511.
HKAKF79	316	909810	1 - 391	15 - 405		R19231, R18719, and H15287.
HKAIK82	317	779306	1 - 697	15 - 711		AI580045, AW081071, R09608, R09503, R98757, AL121657, AC010205, AC005409, AC007151, AC005585, AC004216, AC005102, AC002117, U91321, AC004893, AC003678, AC002302, AL049569, AC002299, AL035555, AL024507, AF124730, AC005041, AC008372, AC005726, AF001548, and AC004997.
HKAHP85	318	783955	1 - 438	15 - 452		W86443.
HKAHI69	319	916528	1 - 623	15 - 637		W73222, R83480, N28346, W23455, W68574, AI913731, AA680399, AW387743, and AF083110.
HKAHE93	320	791860	1 - 352	15 - 366		R44840, AI024922, and R40800.
HKAHA10	321	857339	1 - 324	15 - 338		AA080986, and AB018263.
HKAGC23	322	912677	1 - 485	15 - 499		H53304, H44988, R61405, AA308493, AA339315, AA334068, W56452, F06262, AA470955, AW408162, AA216667, AI925255,

					H38002, AI952095, AI310237, AA428952, M79308, L04966, and X80333.
HKAFR01	323	916400	1 - 386	15 - 400	AA907150, AA907120, AW102570, AA737188, AI248890, and AL137567.
HKAFAQ61	324	741786	1 - 628	15 - 642	R12352, and H93907.
HKA FN96	325	796361	1 - 408	15 - 422	AW135161, AI659980, T12381, AI830387, R86060, AI814646, AI244395, AI439551, AI831637, and AW136645.
HKA FD03	326	924048	1 - 525	15 - 539	AA767865, AW448919, AA502991, AI358089, AA485482, N23504, AW243793, AA302754, AI623764, AA516233, AA483973, AI612142, AA487475, AA122183, AC007993, AC000085, AC005562, AC006312, AF064861, AC006011, M87914, Z82244, AL121655, AC006344, AL109952, AC003006, AC007842, AC006241, AL049872, AC007226, AL035495, AC005273, AC005837, AC004656, AF053356, S42653, AP000251, AL031282, AC004686, AL031432, AC005399, AC004655, AC004895, AC005409, AL034418, AP000030, AP000047, AP000403, U85195, AC005899, AL078593, AC004491, Z83826, AL049543, AC007371, AP000689, AC005004, AC005280, AC003037, AL050321, AE000658, U95742, AC005722, AC004596, AB003151, AP000688, AC006468, AC000025, AC004638, AC005527, AC005632, AC007216, AP000509, AB023049, AC006146, AP000115, AC004253, AL035400, AF001549, AL023803, AL035467, AC004805, AL035422, AF207550, AP000356, AC004859, AL022313, AL049540,

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HKAEJ79	327	917408	1 - 164	15 - 178		T65484, and Z98258.
HKAEG61	328	925951	1 - 435	15 - 449		AA587766, AA534542, AI271683, AA565889, AA143726, AW138648, AA079779, AA595313, AI373637, AI912050, AI912061, AW381284, W40369, AA436795, AW371409, AW371414, T35070, AI024888, AA581215, AW371416, AA902858, and AW177721.
HKADR84	329	800106	1 - 316	15 - 330		AA294984, and AL137694.
HKADP50	330	971356	1 - 1135	15 - 1149		AL119396, AW392670, AL119324, AL119497, AW384394, AW363220, AL119443, Z99396, AW372827, AL119335, AL119319, U46347, U46341, AL119457, AL119496, AL119484, AL119363, AL119341, AL119391, AL119355, U46350, U46351, U46349, AL119399, AL119444, AL119483, U46346, AL119439, AL119522, AL134533, AL134528, AL037205, U46345, AL042450, AL042614, AL134527, AL134538, AL119418, AL134529, AL042965, AL042975, AL042542, AL119511, AL042544, AL042970, AL039912, AL043019, AL042984, AL043029, AL043003, AL042551, AL119488, AL119464, AB026436, AR069079, AR054110, A81671, AR060234, and AR066494.
HKADP11	331	966941	1 - 525	15 - 539		AW297245, AI498295, AI474786, AI002508, U73646, and U73642.
HKADO84	332	911567	1 - 402	15 - 416		AA112539.

HKADG12	333	638194	1 - 327	15 - 341	AI927288, AI651332, AI581184, and AA766507.
HKACX88	334	970793	1 - 289	15 - 303	AI688729, AL042551, AL039390, AI249936, U46348, AL046681, AL047188, AL046137, AI446483, AI672187, AL045166, AI049726, AA598862, AI920975, and AW392669.
HKACX62	335	744273	1 - 659	15 - 673	R88868.
HKACX25	336	678045	1 - 569	15 - 583	AA011530.
HKACU02	337	919850	1 - 643	15 - 657	H65902, AW237443, AI523672, W56193, and AL031259.
HKACP26	338	422255	1 - 522	15 - 536	AA146675.
HKACP23	339	881718	1 - 429	15 - 443	
HKACO69	340	614156	1 - 367	15 - 381	AI817581, AI982574, AL041419, AF037261, and AF064807.
HKACO22	341	674494	1 - 675	15 - 689	T96147.
HKACL83	342	881711	1 - 559	15 - 573	AI337437, and H29102.
HKACK91	343	789430	1 - 331	15 - 345	AA878387, AI951674, D53304, AA598614, T17249, AW080441, AW167496, R88441, D81193, AI702964, and AC004150.
HKACI41	344	924045	1 - 377	15 - 391	AA160816, and AA147147.
HKABY40	345	650852	1 - 449	15 - 463	T73993, AA443150, R54539, F12438, R11740, Z44720, N89128, and AC005520.
HKABW75	346	973331	1 - 133	15 - 147	
HKABU90	347	788888	1 - 569	15 - 583	AI470174, AW085533, AI167938, H97813, AA844268, AI354912, AA834557, AW150903, AA905325, AA948466, AI191066, AA199940, and AW296378.
HKABR92	348	879400	1 - 299	15 - 313	W84513, AI701108, W84525, and AC005237.
HKABQ76	349	857381	1 - 748	15 - 762	AI804230, N69876, N98849, AI719104, and AC003966.

HKABM34	350	703452	1 - 480	15 - 494	AA169857, Z81369, AL079295, and AF153482.
HKABE53	351	892078	1 - 560	15 - 574	AI290663, AA292575, AA451993, AA464348, AW405405, AA297985, R18801, T77313, AA297912, AA057265, R78273, AW405591, F13348, AA310646, N76224, N44152, AW402676, AI907739, and N44162.
HKAAD24	352	787545	1 - 503	15 - 517	R17399, H80368, AA400530, AA480020, AL036571, AA309105, H79194, AW407394, AA316507, AA336787, AA336687, AA069355, AB018307, Z58264, and Z64941.
HFEBY03	353	973292	1 - 686	15 - 700	
HFEBQ59	354	739355	1 - 391	15 - 405	AA428048.
HFEBP01	355	916728	1 - 488	15 - 502	F11460, and AA091955.
HFEBJ61	356	576092	1 - 341	15 - 355	AC006205.
HFEBH07	357	953523	1 - 452	15 - 466	T92504, and T92501.
HFEBD01	358	916725	1 - 324	15 - 338	AA493702.
HFEB A06	359	935685	1 - 399	15 - 413	AA078523, AI911149, AI935709, AI888883, and AC004889.
HFEAU06	360	960609	1 - 433	15 - 447	AI188719, R70967, and AW083352.
HFEAN03	361	925408	1 - 233	15 - 247	AA984600.
HFEAJ78	362	855319	1 - 631	15 - 645	AA340115, AA303007, AA298969, AI135357, AW303096, AW268291, AA595499, AI216990, AI254913, AA912287, AW168420, AI054333, AI932599, AI460009, AA188664, H23653, AA640410, AA640430, AW020599, AI254779, AA972809, AA284247, AA757775, AL046519, AW271904, AA679532, AW021154, AI345157, AA225956, AW069227, AW270258, AA468131, AW103509, AA507824, F12561, AA610373, AI820920, T59612, AA533762,

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HFEAI72	363	700631	1 - 435	15 - 449	AP000044, AP000112, AC005837, AC004087, AC005520, AC004851, Z98044, and AL022476. H19656, AI871221, N53491, AA340081, AI476773, R02223, AA019169, AA044939, AA021017, H37973, W96236, R74403, R74224, AA016157, AI762534, AI201941, AA017120, AA015837, H42352, AW000821, T63666, AA476232, AA873589, AI095887, AI357647, AI445981, AI261809, AA279231, U73637, AF015416, AL137276, and AF083108.
HFEAI49	364	722129	1 - 485	15 - 499	AA284260, W48785, AI131081, W49755, AW069789, AI023062, AA340065, AW206500, AF086202, Y16790, and AC003958.
HFEAH01	365	916068	1 - 496	15 - 510	AA704235.
HFEAG41	366	504596	1 - 426	15 - 440	AI190071, AA009967, AI274239, AI288530, AI160067, AA009968, W02653, AI264920, AA456003, AA339939, and AA455358.
HESAC55	367	518730	1 - 55	15 - 69	
HESAC45	368	537453	1 - 210	15 - 224	Z97200.
HERAS77	369	772471	1 - 306	15 - 320	AI557808, AI557426, AI557602, AI541027, AI541075, AI541048, AI557543, and AI535994.
HERAS69	370	974532	1 - 495	15 - 509	
HERAN59	371	739562	1 - 325	15 - 339	T82116, AI829904, AA631175, R00898, AA833920, T85082, and AF187320.
HERAN52	372	855536	1 - 362	15 - 376	H55872, and H54532.
HERAN24	373	855537	1 - 363	15 - 377	T87555, and AL021391.
HERAN16	374	973714	1 - 161	15 - 175	
HERAN06	375	954671	1 - 542	15 - 556	AA601241.
HERAL72	376	529196	1 - 300	15 - 314	AP000280, AP000039, and AP000107.
HERAK96	377	796591	1 - 208	15 - 222	AA601268, N23705, AC007567, AF172277,

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HERAK20	378	855546	1 - 378	15 - 392	AA903174, AA699307, AA233864, AA809473, AA649328, AL035416, and AL132776.
HERAK01	379	921634	1 - 465	15 - 479	AA482969.
HERAH85	380	928415	1 - 489	15 - 503	AW378532, AW169038, AA641651, AA847499, AA570740, AA483606, AA568204, AW069227, AW303098, AA721645, AL042667, AL042670, H07953, AI278972, AA757426, AI755214, AI733856, AA773463, AI687343, AI369580, AA453558, AI754567, AA613761, AL120282, H73550, AI627614, AW301736, AA828153, AA410788, AA749235, AI859438, AW270385, AI754105, AA704393, T74524, AA630854, AA828637, AI056177, AA491767, AA315361, AI634187, AI431513, AA634991, AA527877, AA113272, AI310464, AA502991, AI457313, AA056248, AA515939, AI620992, AA630923, AI565084, AA579205, H69765, AA176604, T47138, AI580652, AA228778, AI077941, AI038304, AI249688, AA426277, AI754336, T50676, AA084609, AI433104, AI143840, AW188427, AL120141, W23546, R94326, AI277783, AA744094, AI569100, AI679002, AI860020, AA744048, AA613630, AA535216, AI564201, AA558366, AA598605, AA904211, AA713765, AI268019, AW338021, R99532, AI380617, H60912, AA640710,

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HERAH37	381	707573	1 - 770	15 - 784	H19029.
HERAH16	382	880475	1 - 551	15 - 565	AI633346.
HERAH06	383	954672	1 - 1054	15 - 1068	AW296421, AA827698, AA485215, AI684418, AA484940, AA907560, AI434764, AA808137, AA725527, AA931349, AI473248, AA479094, T06094, and AA827660.
HERAG53	384	728441	1 - 319	15 - 333	AA923410, H90248, and AC004985.
HERAE59	385	739569	1 - 405	15 - 419	AA021495.
HERAE24	386	678518	1 - 541	15 - 555	T54292.
HERAD94	387	793020	1 - 382	15 - 396	H87576.
HERAD26	388	520370	1 - 486	15 - 500	AA533241, AI824558, AW082490, AA745348, AI241976, AP001053, Z93017, AF001548, AC003043, AF053356, AC004491, AL031670, AC002551, AC005086, AP000553, AL049869, AL034417, AC016025, AC003010, AF047825, AC004890, AC005697, AP000355, AC007546, AC007845, AC005562, AL034423, AC009516, AC004966, AL080243, AL034420, AC005210, AC004383, AC005529, AF196970, AC004851, AJ003147, AL121603, AL031681, AP000501, AC002300, Z95152, AC005015, AC004805, AC006441, AC002094, AC008124, Z83822, AC005488, AC005261, AC005722, AC005406, U82828, AC002126, AC005081, AP000011,

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HERAC89	389	787123	1 - 412	15 - 426	H60777, AI285970, AA654046, and AC002040.
HERAB53	390	727373	1 - 413	15 - 427	R48728.
HBIPD10	391	961972	1 - 144	15 - 158	T78780, AL118680, and Z83843.
HBIPB07	392	951981	1 - 330	15 - 344	N92182.
HBIOZ10	393	973131	1 - 490	15 - 504	
HBIOW11	394	965551	1 - 563	15 - 577	AA031463, and AA027921.
HBLOT01	395	914657	1 - 728	15 - 742	AA573622, R08736, and AA573669.
HBLOM94	396	973137	1 - 1128	15 - 1142	AW369756, AW062278, AA452837, AA452978, AI767361, AI005282, AI263850, AW016065, N62955, AA514551, AI674818, and AA885328.
HBIOI47	397	973132	1 - 506	15 - 520	
HBIOJ05	398	930754	1 - 533	15 - 547	AW295399, AW170383, AA600968, AA778832, AW300641, AW070290, AW207772, AW392670, AL119355, AL119483, U46349, AL119319, AL119457, AW372827,

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HBIOF05	399	930771	1 - 792	15 - 806	AI023133, AA745668, T87533, T72340, T87532, T61876, and AC004832.
HBIMT11	400	965089	1 - 662	15 - 676	AA404261, L44574, AI526093, AF083391, and Z68164.
HBIMR08	401	957996	1 - 452	15 - 466	AI082567, AI803534, AI479326, AA005385, and AA002250.
HBFA23	402	504560	1 - 193	15 - 207	AA321091, AA321090, and AW194192.
HAWCB26	403	685045	1 - 603	15 - 617	AA037375, AI494120, AA004786, and AA320986.
HAWAZ32	404	702976	1 - 450	15 - 464	AA081658, AI823374, and AA320822.
HAWAY15	405	829255	1 - 507	15 - 521	AA320756, N76958, AI337184, N76959, T30637, H83591, AI279487, T24591, R36246, R33788, AA349213, AI223852, AW135460, R58021, T31602, AA211453, Z17873, R57086, and AF094583.
HAWAW12	406	971497	1 - 482	15 - 496	AA320662, AA115655, and AA613188.
HAWAS28	407	416137	1 - 516	15 - 530	AW444450, AW452191, AW297700, N95486, AA320488, AA706097, R81942, AW029388, and AJ001189.
HAWAQ06	408	960762	1 - 667	15 - 681	T97076, AA593256, and AA320405.

HAWAA53	409	864417	1 - 414	15 - 428	AI904861, N50472, and AA319938.
HAVAF22	410	675054	1 - 315	15 - 329	T68116.
HAVAC03	411	925291	1 - 529	15 - 543	AA700867, AA780053, AA701583, W92785, AA693772, AW191053, AI696700, AI678951, AI918899, AI972441, and AC005221.
HARNOS4	412	729117	1 - 419	15 - 433	H23546.
HARNI55	413	731232	1 - 461	15 - 475	R98614, and T62742.
HARND69	414	754675	1 - 600	15 - 614	AI186548, AA436545, AA425059, AA025411, AI167560, AA918182, AI184458, AA897280, and AI168373.
HARNB30	415	731614	1 - 409	15 - 423	AA193632, and R00325.
HARMV85	416	864612	1 - 442	15 - 456	AA601359, and AC007388.
HARMP93	417	791948	1 - 517	15 - 531	R85588.
HARMM53	418	854369	1 - 505	15 - 519	H17278, R54233, AA343867, AA127371, AW402213, W31401, N57391, W69274, AA121905, N45642, AA308042, AA346816, AA173466, AW378674, AA102012, T32519, N53800, T19064, AB018285, and X59993.
HARMA51	419	725137	1 - 338	15 - 352	H65776, H65775, R00579, and D29222.
HADXB70	420	757287	1 - 442	15 - 456	T82184.
HADGI45	421	717755	1 - 536	15 - 550	AI799976, AI640342, AI813303, AI493125, AW074863, AI808051, AA151242, AI520688, AA151243, AW138657, AA677631, H63202, AI270648, AI052606, H63116, AI061381, AI885928, and AI659159.
HADGG22	422	674421	1 - 866	15 - 880	AI810674, AW297801, AA678903, R62179, AA631103, T83658, AW090118, AA528329, T98059, R92773, R64568, and T97982.
HADGC96	423	865247	1 - 369	15 - 383	H75641.
HADGB52	424	647367	1 - 540	15 - 554	AI097624, AI431774, AI741173, AI478836,

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HADGB01	425	916374	1 - 508	15 - 522	T88730, AA825224, and W90089.
HADFZ81	426	420937	1 - 391	15 - 405	AA085117, AA878759, and H84305.
HADFZ14	427	848980	1 - 662	15 - 676	W86243, AW074332, AW006527, AA347495, AA776663, AA573067, AL036949, AW275640, AA578326, AA688303, AI668951, AA601084, AL044758, AI174703, AI364984, AI270280, AA594742, AA584738, AW452106, AA180056, AL047685, AA916556, AA557508, AA657808, AA427747, AA640305, AA715848, AA492496, T57562, AI143244, AA846944, AW169183, AI741059, AW162314, AW162332, AA598741, T49381, AA578711, AA584241, AA587550, AI114851, AI918550, AI797998, AW268052, T95537, AW301438, AA669225, AA687565, AA568303, R07491, AA568311, AW020682, AI133656, H05742, AL138119, AA857823, AA731859, AA493464, AW247955, AA425283, H16231, R12765, W60535, AW409621, AA780818, AA209188, H60489, AA088900, AI310670, AA112864, AI955861, AA493477, AW273177, AA480561, AI275631, AA525807, AW361157, AI745666, AW273235, AA569565, AA528507, AI869094, AW069273, AI952885, N73337, AI051775, AL044438, AA525071,

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HADFW15	428	848983	1 - 665	15 - 679	AA077785.
HADFW06	429	935340	1 - 451	15 - 465	AA192731, AA192764, AA985199, R95840, N72170, N26201, F00564, AL048275, AA470567, AA992908, H60249, AA297670, H53217, AW162442, AA559241, AA654778, H66577, AW188742, AI635440, AI912401, AI054030, AW419389, AL044340, AA533054, AI307565, AI344948, AA856851, AI418661, AA182731, AW083678, AI499954, H73550, AI669421, AI491725, AA579188, AA618140, AC004150, AC004797, AL031005, AC006254, AC007225, AF196779, AL133246, AL020993, AL031315, AL031311, AF001550, AC005488, AC007263, AC004686, AC006544, AC006449, AC005284, AC006505, Z83826, AC007685, AC005899, AC005225, AL031662, Z83840, AC002546, AC007262, AC007686, AL031291,

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HADFV03	430	972437	1 - 424	15 - 438	
HADFT70	431	757158	1 - 336	15 - 350	R28490.
HADFJ08	432	959297	1 - 523	15 - 537	AA721097, Z43838, and AC004850.
HADFG90	433	788865	1 - 441	15 - 455	T87517, T87516, T78515, and T79855.
HADFD69	434	754277	1 - 457	15 - 471	AA164604, F07672, AF155115, and AC004890.
HADFC15	435	659541	1 - 387	15 - 401	N98316, AW000995, and AI748897.
HADFB60	436	740318	1 - 437	15 - 451	AI690274, AI492203, AA401279, AA404246, N48627, AI276004, AI024988, AW007396, AW074066, AI032465, AA773647, AA630603, AW169623, AI659076, AW016276, AI810405, and AI701343.
HADFB55	437	731686	1 - 504	15 - 518	R74442, and AC006991.
HADFB08	438	959273	1 - 348	15 - 362	AC007385.
HADEY09	439	625505	1 - 266	15 - 280	AA054766.

HADEU65	440	747880	1 - 593	15 - 607	AI986400, and H81086.
HADEU32	441	699194	1 - 503	15 - 517	AI701480, AA101386, and C01275.
HADET68	442	906389	1 - 755	15 - 769	AA190865, W69970, AI382438, N25872, AI873741, W99370, AI187156, AW088488, AI969940, AI088449, AI631818, AI311717, AW205456, AA398256, AA830014, AA811798, AI796467, AI452434, AI159823, AA158516, AA225625, W92243, N30762, R59937, AW137104, AA761003, AA634216, AA146624, AI278434, AA535733, AI494095, AI052585, AI859053, AI479960, AW024960, AI066392, AI718153, AA564062, AA034276, AI245054, N35034, AI906964, AW338143, W92242, and AI708811.
HADDS75	443	660816	1 - 449	15 - 463	AI372645, AI133330, AI301214, N31372, AI290759, H48745, H73512, AW021317, AI114633, W68505, W02524, AA039465, T83388, W16941, H60571, N21416, T56163, R01722, T99408, H50816, N38741, W31528, AA148484, AW439245, N80913, W86241, AI186806, AI740935, R86061, AA493422, AW003391, AI743264, AA564635, AA779666, AA843877, AI022120, AI188150, AA452018, AI184622, AA877163, AA627862, AI057547, AI120253, AI150812, AI469111, AI222801, AA367284, W16907, AI589760, AW380519, AI491889, N66738, AA854842, AI872089, AA365891, X85693, AW276304, AW410492, AI150758, N57546, AI366719, AA574215, AA039466, H46102, N54433, AA985543,

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HADDS21	444	670802	1 - 214	15 - 228	AI142134, AL038838, AL037436, AL038983, AL038822, AL037727, AL038532, AL037295, AL040617, AL044186, AL041238, AL047012, AL037435, AL044125, AL044037, AL045817, AL047170, AL040463, AL040576, AL037343, AL045753, AL041752, AL045684, AL040625, AL047219, AL041635, AL044162, AL041602, AL043492, AL040839, AL043677, AL040193, AL043467, AL040510, AL037335, AL043923, AL043814, AL040621, AL043538, AL047183, AL043496, AL040464, AL037323, AL040294, AL043845, AL046442, AL044074, AL037443, AL041133, AL044064, AL041324, AL041459, AL041577, AL040075, AL041347, AL040322, AL040149, AL041098, AL040052, AL041730,

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HADDS07	445	849000	1 - 291	15 - 305		R08444, N40963, N46826, AA640680, AA657537, AC005081, AC002091, AC005015, AL049694, AC004139, AC006388, and AB026898.
HADDR20	446	669609	1 - 446	15 - 460		AA262058.
HADDQ56	447	733340	1 - 473	15 - 487		N63670, and H52048.
HADDP12	448	970537	1 - 438	15 - 452		
HADDI89	449	865278	1 - 426	15 - 440		R08068, H90688, AA984920, AA828045, AL139054, AC005562, AC006111, AC004813, AF053356, AL033376, AC002470, AC005899, AC006960, AC002425, AC004967, AC007993, AC005015, AL022165, AC003950, AC004125, AC005531, AL049569, U07000, AB023048, AP000010, AL049779, AC004382, AC008372, AC006023, AL022320, AL096774, AC007216, U95742, AF038458, AL050307, and AC006285.
HADDI54	450	729760	1 - 446	15 - 460		
HADDI42	451	713700	1 - 103	15 - 117		AA968485, AC002527, AP000550, AC008149, AC008080, AL049631, AL136295, AC008018, AC012330, AC007685, AC007325, Z95325, AL133355, AC007981, AC004491, AC005821, U85195, AE000658, AC007708, AL024507, and AC006057.
HADDE27	452	683382	1 - 372	15 - 386		R38342.
HADDE15	453	952542	1 - 776	15 - 790		AI744486, AA903456, AW068237, AA643634, R92952, AW364719, H75941, AA039352, and AA039428.
HADDC94	454	794266	1 - 558	15 - 572		H43867, AA780295, AA481208, AW337577,

						AA836333, AW268859, AI887751, D62679, and D79824.
HADDC64	455	469113	1 - 468	15 - 482		AA778816, AI022235, and AI912111.
HADDC44	456	715928	1 - 452	15 - 466		
HADDC42	457	713657	1 - 458	15 - 472		
HADDC05	458	932066	1 - 482	15 - 496		
HADDB62	459	743476	1 - 518	15 - 532		
HADDB13	460	657120	1 - 442	15 - 456		
HADDA04	461	925627	1 - 333	15 - 347		
HADCZ08	462	959304	1 - 421	15 - 435		AA578523, N69399, AI364568, AI272649, AW265274, T52745, AA159006, AA547979, T02827, AL047480, W81372, H68343, AI570019, AI744830, AA565911, AA664126, AA508148, M78026, F00350, AA357878, R55078, AA847710, AI054090, AI246061, AA356310, F33126, AA984585, F33494, AA150013, AA487226, AA297776, AI678812, AI689029, N27874, AI376197, AA663030, AI567941, AA453127, AI679394, AI925423, AA503018, Z99716, AC020663, AL049699, AC006581, D88270, AF126403, AC004983, Z83826, AC005316, D86992, AL049779, AC005317, AC004491, AL021397, AC004659, AC004801, AC015853, AP000031, AC006035, AC006441, AC005089, U52111, U51561, AC006313, AC006021, AL031432, AC005740, AC012384, AC005218, AC005250, AC004079, AP000555, AL035405, AL139054, AL049694, AC005088, Z95115, AF124523, AL035587, AC004223, AC005210, AC005180, AL049761,

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HADCX34	463	704030	1 - 492	15 - 506		N46092, and N49191.
HADCW01	464	916399	1 - 504	15 - 518		AA293532, H53687, AW291311, T49748, and AA780313.
HADCP73	465	764391	1 - 448	15 - 462		
HADCP50	466	723684	1 - 446	15 - 460		AC004788.
HADCO30	467	914688	1 - 314	15 - 328		W68180, AA777538, AI016897, AA505811, AI804007, AA211372, AA262276, H30038, AA573625, AI333526, T86707, AW449911, and W94803.
HADCO03	468	924043	1 - 494	15 - 508		AA028096, AA235869, and AC003963.
HADCN29	469	690600	1 - 552	15 - 566		AA418028, and AI401479.
HADCH77	470	826137	1 - 657	15 - 671		R91980, H94853, and AC002395.
HADCD46	471	719005	1 - 529	15 - 543		AA054485, AA114892, AA058522, and AA114893.
HADAY29	472	690602	1 - 313	15 - 327		N67971.
HADAS83	473	490455	1 - 465	15 - 479		AA582073, AW277171, T08298, AL044286, N73855, AW172928, AA988601, AI275071, AA953238, AA724782, W92132, AI564454, AA668807, AA492391, AA572812, AA188670, AA362511, AW360894, AI635247, AC005071, Z93930, AC007707, AL109654, AC005212, AL008637, AC006040, AF107885, AF045555, AJ011930, AL031846, AI109985, AC004816,

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HADAR23	474	675844	1 - 908	15 - 922	H70932, H71018, AA644669, and AL096772.
HADAM60	475	740326	1 - 381	15 - 395	T63452.
HADAE96	476	796469	1 - 382	15 - 396	H50907, H50917, and H50938.
HADAE92	477	792823	1 - 459	15 - 473	R34471, AW021062, and AC005856.
HACCW79	478	774898	1 - 440	15 - 454	N57511, AW169153, N34512, AI677832, N33099, D60324, AW247893, D81067, AI867484, H83428, AW044454, AI869047, AA426226, AI080402, AI590805, AI393129, AA159625, AA934072, AI359017, AA736535, AA782955, AA150219, AW248839, AW291088, AI824032, AA136239, AA143058, AW134681, AI937151, AI720406, AA037761, AA136326, AW242313, N44915, AF161487, and AF161527.
HACCT11	479	966886	1 - 335	15 - 349	AA742786, AC004765, and AC004254.
HACBW76	480	849054	1 - 502	15 - 516	AA534725, C14805, and AI824978.
HACBU26	481	683006	1 - 826	15 - 840	AI923119, AI884571, AA910503, AW327469, AW148606, AI334355, AI538884, AA595725, AI310084, AA256652, AI422677, AI291710, AI356846, R99346, AA633060, N30667, AW327470, AA280603, AI610334, AI349093,

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HACBO10	482	964459	1 - 703	15 - 717	AI732190, AI821730, AI935265, AA931721, AA598488, AI821204, AA653397, AA872260, AJ006995, and AC009721.
HACBN71	483	872015	1 - 457	15 - 471	N36051, N33866, H42954, AA411585, AA485512, AW407316, AA477803, D81930, N79656, AA393178, H93834, AI908551, AI908565, AA298404, AA143285, AA296690, AI910113, AA297564, AA303056, AA296812, AA296976, AA045562, W21048, AI031665, AW276772, AA082648, AW001391, AI066608, AA298311, AI290747, AA305827, R97588, AA297445, AI186832, AI147480, AI084670, AI140421, and AI720871.
HACBI83	484	875263	1 - 460	15 - 474	H30314, N33882, R50257, R50650, AA235113,

					AA283851, AA489709, AF126164, and AF126163.
HACBJ17	485	663371	1 - 481	15 - 495	H15324, H15325, R21298, and AL049713.
HACBH42	486	933951	1 - 513	15 - 527	AA456485, AA234642, W30931, AF124251, AF168364, and AB030442.
HACBB13	487	698800	1 - 418	15 - 432	H74233, AW205784, AA157880, AI581278, AA134927, AI418897, AA385998, AW172419, AW341704, AA325637, AA158718, AA931407, AI199564, AA693922, AA807889, AA932838, AI002537, T96136, AW083925, AI830223, AI914970, AA978020, AA861149, AA744572, AI261752, AA150534, AA835679, AA804787, F16852, AA873015, AW117276, AA729420, AI611192, AA699638, AI351776, AA203423, AA317352, AA203456, AI961898, H00617, AA906614, H01783, R62542, AA324813, AA886983, AA700174, AA973939, AA247331, AA887599, AI799375, H97221, AW167067, R24697, Z45479, AI313028, AI345360, AW304568, AI312388, AI252594, AI251182, AI312285, AI583295, AA385999, AI054032, AW271901, AA970565, AA321756, AI144033, AI144109, AA703148, AW271131, AW271148, T99095, AA364223, AA384273, W01014, AA627126, W32401, and AA545762.
HACAB93	488	792382	1 - 496	15 - 510	AA258113.
HACAA57	489	733887	1 - 498	15 - 512	AW418522, AI922912, AA001450, D81693, D60730, H85556, D80496, C15251, D80929,

TABLE 4

Code	Description	Tissue	Organ	Cell Line	Disease	Vector
AR022	a Heart	a Heart				
AR023	a Liver	a Liver				
AR024	a mammary gland	a mammary gland				
AR025	a Prostate	a Prostate				
AR026	a small intestine	a small intestine				
AR027	a Stomach	a Stomach				
AR028	Blood B cells	Blood B cells				
AR029	Blood B cells activated	Blood B cells activated				
AR030	Blood B cells resting	Blood B cells resting				
AR031	Blood T cells activated	Blood T cells activated				
AR032	Blood T cells resting	Blood T cells resting				
AR033	brain	brain				
AR034	breast	breast				
AR035	breast cancer	breast cancer				
AR036	Cell Line CAOV3	Cell Line CAOV3				
AR037	cell line PA-1	cell line PA-1				
AR038	cell line transformed	cell line transformed				
AR039	colon	colon				
AR040	colon (9808co65R)	colon (9808co65R)				
AR041	colon (9809co15)	colon (9809co15)				
AR042	colon cancer	colon cancer				
AR043	colon cancer (9808co64R)	colon cancer (9808co64R)				
AR044	colon cancer 9809co14	colon cancer 9809co14				
AR045	corn clone 5	corn clone 5				
AR046	corn clone 6	corn clone 6				
AR047	corn clone2	corn clone2				
AR048	corn clone3	corn clone3				
AR049	Corn Clone4	Corn Clone4				
AR050	Donor II B Cells 24hrs	Donor II B Cells 24hrs				
AR051	Donor II B Cells 72hrs	Donor II B Cells 72hrs				
AR052	Donor II B-Cells 24 hrs.	Donor II B-Cells 24 hrs.				
AR053	Donor II B-Cells 72hrs	Donor II B-Cells 72hrs				
AR054	Donor II Resting B Cells	Donor II Resting B Cells				
AR055	Heart	Heart				
AR056	Human Lung (clonotech)	Human Lung (clonotech)				
AR057	Human Mammary (clonotech)	Human Mammary (clonotech)				
AR058	Human Thymus (clonotech)	Human Thymus (clonotech)				
AR059	Jurkat (unstimulated)	Jurkat (unstimulated)				
AR060	Kidney	Kidney				
AR061	Liver	Liver				
AR062	Liver (Clontech)	Liver (Clontech)				

AR063	Lymphocytes chronic lymphocytic leukaemia	Lymphocytes chronic lymphocytic leukaemia				
AR064	Lymphocytes diffuse large B cell lymphoma	Lymphocytes diffuse large B cell lymphoma				
AR065	Lymphocytes follicular lymphoma	Lymphocytes follicular lymphoma				
AR066	normal breast	normal breast				
AR067	Normal Ovarian (4004901)	Normal Ovarian (4004901)				
AR068	Normal Ovary 9508G045	Normal Ovary 9508G045				
AR069	Normal Ovary 9701G208	Normal Ovary 9701G208				
AR070	Normal Ovary 9806G005	Normal Ovary 9806G005				
AR071	Ovarian Cancer	Ovarian Cancer				
AR072	Ovarian Cancer (9702G001)	Ovarian Cancer (9702G001)				
AR073	Ovarian Cancer (9707G029)	Ovarian Cancer (9707G029)				
AR074	Ovarian Cancer (9804G011)	Ovarian Cancer (9804G011)				
AR075	Ovarian Cancer (9806G019)	Ovarian Cancer (9806G019)				
AR076	Ovarian Cancer (9807G017)	Ovarian Cancer (9807G017)				
AR077	Ovarian Cancer (9809G001)	Ovarian Cancer (9809G001)				
AR078	ovarian cancer 15799	ovarian cancer 15799				
AR079	Ovarian Cancer 17717AID	Ovarian Cancer 17717AID				
AR080	Ovarian Cancer 4004664B1	Ovarian Cancer 4004664B1				
AR081	Ovarian Cancer 4005315A1	Ovarian Cancer 4005315A1				
AR082	ovarian cancer 94127303	ovarian cancer 94127303				
AR083	Ovarian Cancer 96069304	Ovarian Cancer 96069304				
AR084	Ovarian Cancer 9707G029	Ovarian Cancer 9707G029				
AR085	Ovarian Cancer 9807G045	Ovarian Cancer 9807G045				
AR086	ovarian cancer 9809G001	ovarian cancer 9809G001				
AR087	Ovarian Cancer 9905C032RC	Ovarian Cancer 9905C032RC				
AR088	Ovarian cancer 9907 C00 3rd	Ovarian cancer 9907 C00 3rd				
AR089	Prostate	Prostate				
AR090	Prostate (clonotech)	Prostate (clonotech)				
AR091	prostate cancer	prostate cancer				
AR092	prostate cancer #15176	prostate cancer #15176				
AR093	prostate cancer #15509	prostate cancer #15509				
AR094	prostate cancer #15673	prostate cancer #15673				

AR095	Small Intestine (Clontech)	Small Intestine (Clontech)				
AR096	Spleen	Spleen				
AR097	Thymus T cells activated	Thymus T cells activated				
AR098	Thymus T cells resting	Thymus T cells resting				
AR099	Tonsil	Tonsil				
AR100	Tonsil germinal center centroblast	Tonsil germinal center centroblast				
AR101	Tonsil germinal center B cell	Tonsil germinal center B cell				
AR102	Tonsil lymph node	Tonsil lymph node				
AR103	Tonsil memory B cell	Tonsil memory B cell				
AR104	Whole Brain	Whole Brain				
AR105	Xenograft ES-2	Xenograft ES-2				
AR106	Xenograft SW626	Xenograft SW626				
H0068	Human Skin Tumor	Human Skin Tumor	Skin		disease	Uni-ZAP XR
H0081	Human Fetal Epithelium (Skin)	Human Fetal Skin	Skin			Uni-ZAP XR
H0086	Human epithelioid sarcoma	Epithelioid Sarcoma, muscle	Sk Muscle		disease	Uni-ZAP XR
H0344	Adipose tissue (human)	Adipose - 6825A (human)				Uni-ZAP XR
H0345	SKIN	Skin - 4000868H	Skin			Uni-ZAP XR
H0427	Human Adipose	Human Adipose, left hiplipoma				pSport1
H0443	H. Adipose, subtracted	Human Adipose, left hiplipoma				pSport1
H0494	Keratinocyte	Keratinocyte				pCMVSPORT 2.0
H0540	Skin, burned	Skin, leg burned	Skin			pSport1
H0548	Human Skin Fibroblasts, normal	Human Skin Fibroblasts				pBluescript
H0586	Healing groin wound, 6.5 hours post incision	healing groin wound, 6.5 hours post incision - 2/	groin		disease	pCMVSPORT 3.0
H0587	Healing groin wound; 7.5 hours post incision	Groin-2/19/97	groin		disease	pCMVSPORT 3.0
H0592	Healing groin wound - zero hr post-incision (control)	HGS wound healing project; abdomen			disease	pCMVSPORT 3.0
H0593	Olfactory epithelium;nasalcavity	Olfactory epithelium from roof of left nasal cavity				pCMVSPORT 3.0
H0600	Healing Abdomen wound;70&90 min post incision	Abdomen			disease	pCMVSPORT 3.0
H0601	Healing Abdomen Wound;15 days post incision	Abdomen			disease	pCMVSPORT 3.0
H0602	Healing Abdomen Wound;21&29 days post incision	Abdomen			disease	pCMVSPORT 3.0
S0040	Adipocytes	Human Adipocytes from Osteoclastoma				Uni-ZAP XR
S0280	Human Adipose Tissue, re-excision	Human Adipose Tissue				Uni-ZAP XR

S0342	Adipocytes;re-excision	Human Adipocytes from Osteoclastoma				Uni-ZAP XR
S0348	Cheek Carcinoma	Cheek Carcinoma			disease	pSport1
S6022	H. Adipose Tissue	Human Adipose Tissue				Uni-ZAP XR
T0001	Human Brown Fat	Brown Fat				pBluescript SK-
T0004	Human White Fat	Human White Fat				pBluescript SK-
T0060	Human White Adipose	Human White Fat				pBluescript SK-
L0005	Clontech human aorta polyA+ mRNA (#6572)					
L0021	Human adult (K.Okubo)					
L0060	Human thymus NSTH II					
L0361	Stratagene ovary (#937217)		ovary			Bluescript SK
L0362	Stratagene ovarian cancer (#937219)					Bluescript SK-
L0363	NCI_CGAP_GC2	germ cell tumor				Bluescript SK-
L0365	NCI_CGAP_Phe1	pheochromocytoma				Bluescript SK-
L0366	Stratagene schizo brain S11	schizophrenic brain S-11 frontal lobe				Bluescript SK-
L0369	NCI_CGAP_AA1	adrenal adenoma	adrenal gland			Bluescript SK-
L0375	NCI_CGAP_Kid6	kidney tumor	kidney			Bluescript SK-
L0376	NCI_CGAP_Lar1	larynx	larynx			Bluescript SK-
L0385	NCI_CGAP_Gas1	gastric tumor	stomach			Bluescript SK-
L0388	NCI_CGAP_HN6	normal gingiva (cell line from immortalized kerati				Bluescript SK-
L0435	Infant brain, LLNL array of Dr. M. Soares INIB					lafmid BA
L0438	normalized infant brain cDNA	total brain	brain			lafmid BA
L0439	Soares infant brain INIB		whole brain			Lafmid BA
L0455	Human retina cDNA randomly primed sublibrary	retina	eye			lambda gt10
L0471	Human fetal heart, Lambda ZAP Express					Lambda ZAP Express
L0483	Human pancreatic islet					Lambda ZAPII
L0517	NCI CGAP Pr1					pAMP10
L0518	NCI CGAP Pr2					pAMP10
L0519	NCI CGAP Pr3					pAMP10
L0520	NCI_CGAP_Alv1	alveolar rhabdomyosarcoma				pAMP10
L0521	NCI CGAP Ew1	Ewing's sarcoma				pAMP10
L0527	NCI CGAP Ov2	ovary				pAMP10
L0532	NCI CGAP Thy1	thyroid				pAMP10
L0539	Chromosome 7 Placental cDNA Library		placenta			pAMP10

L0545	NCI_CGAP_Pr4.1	prostatic intraepithelial neoplasia - high grade	prostate			pAMP10
L0562	Chromosome 7 HeLa cDNA Library			HeLa cell line; ATCC		pAMP10
L0581	Stratagene liver (#937224)		liver			pBluescript SK
L0589	Stratagene fetal retina 937202					pBluescript SK-
L0591	Stratagene HeLa cell s3 937216					pBluescript SK-
L0592	Stratagene hNT neuron (#937233)					pBluescript SK-
L0593	Stratagene neuroepithelium (#937231)					pBluescript SK-
L0594	Stratagene neuroepithelium NT2RAMI 937234					pBluescript SK-
L0595	Stratagene NT2 neuronal precursor 937230	neuroepithelial cells	brain			pBluescript SK-
L0596	Stratagene colon (#937204)		colon			pBluescript SK-
L0598	Morton Fetal Cochlea	cochlea	ear			pBluescript SK-
L0599	Stratagene lung (#937210)		lung			pBluescript SK-
L0600	Weizmann Olfactory Epithelium	olfactory epithelium	nose			pBluescript SK-
L0601	Stratagene pancreas (#937208)		pancreas			pBluescript SK-
L0602	Pancreatic Islet	pancreatic islet	pancreas			pBluescript SK-
L0603	Stratagene placenta (#937225)		placenta			pBluescript SK-
L0604	Stratagene muscle 937209	muscle	skeletal muscle			pBluescript SK-
L0605	Stratagene fetal spleen (#937205)	fetal spleen	spleen			pBluescript SK-
L0608	Stratagene lung carcinoma 937218	lung carcinoma	lung	NCI-H69		pBluescript SK-
L0616	Chromosome 21 exon					pBluescript IKS+
L0637	NCI_CGAP_Brn53	three pooled meningiomas	brain			pCMV- SPORT6
L0638	NCI_CGAP_Brn35	tumor, 5 pooled (see description)	brain			pCMV- SPORT6
L0653	NCI_CGAP_Lu28	two pooled squamous cell carcinomas	lung			pCMV- SPORT6
L0655	NCI_CGAP_Lym12	lymphoma, follicular mixed small and large cell	lymph node			pCMV- SPORT6
L0659	NCI_CGAP_Pan1	adenocarcinoma	pancreas			pCMV- SPORT6
L0662	NCI_CGAP_Gas4	poorly differentiated adenocarcinoma with signet r	stomach			pCMV- SPORT6
L0663	NCI CGAP Ut2	moderately-	uterus			pCMV-

		differentiated endometrial adenocarcino				SPORT6
L0664	NCI_CGAP_Ut3	poorly-differentiated endometrial adenocarcinoma,	uterus			pCMV- SPORT6
L0666	NCI_CGAP_Ut1	well-differentiated endometrial adenocarcinoma, 7	uterus			pCMV- SPORT6
L0667	NCI_CGAP_CML1	myeloid cells, 18 pooled CML cases, BCR/ABL rearra	whole blood			pCMV- SPORT6
L0717	Gessler Wilms tumor					pSPORT1
L0731	Soares_pregnant_uterus NbHPU		uterus			pT7T3-Pac
L0740	Soares melanocyte 2NbHM	melanocyte				pT7T3D (Pharmacia) with a modified polylinker
L0741	Soares adult brain N2b4HB55Y		brain			pT7T3D (Pharmacia) with a modified polylinker
L0742	Soares adult brain N2b5HB55Y		brain			pT7T3D (Pharmacia) with a modified polylinker
L0743	Soares breast 2NbHBst		breast			pT7T3D (Pharmacia) with a modified polylinker
L0744	Soares breast 3NbHBst		breast			pT7T3D (Pharmacia) with a modified polylinker
L0745	Soares retina N2b4HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0746	Soares retina N2b5HR	retina	eye			pT7T3D (Pharmacia) with a modified polylinker
L0747	Soares_fetal_heart_NbH H19W		heart			pT7T3D (Pharmacia) with a modified polylinker
L0748	Soares fetal liver spleen 1NFLS		Liver and Spleen			pT7T3D (Pharmacia) with a modified polylinker
L0749	Soares_fetal_liver_splee n 1NFLS_S1		Liver and Spleen			pT7T3D (Pharmacia)

						with a modified polylinker
L0750	Soares_fetal_lung_NbH L19W		lung			pT7T3D (Pharmacia) with a modified polylinker
L0751	Soares ovary tumor NbHOT	ovarian tumor	ovary			pT7T3D (Pharmacia) with a modified polylinker
L0752	Soares_parathyroid_tumor_NbHPA	parathyroid tumor	parathyroid gland			pT7T3D (Pharmacia) with a modified polylinker
L0754	Soares placenta Nb2HP		placenta			pT7T3D (Pharmacia) with a modified polylinker
L0755	Soares_placenta_8to9weeks_2NbHP8to9W		placenta			pT7T3D (Pharmacia) with a modified polylinker
L0756	Soares_multiple_sclerosis_2NbHMSP	multiple sclerosis lesions				pT7T3D (Pharmacia) with a modified polylinker V_TYPE
L0757	Soares_senescent_fibroblasts_NbHSF	senescent fibroblast				pT7T3D (Pharmacia) with a modified polylinker V_TYPE
L0758	Soares_testis_NHT					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0759	Soares_total_fetus_Nb2 HF8_9w					pT7T3D-Pac (Pharmacia) with a modified polylinker
L0763	NCI_CGAP_Br2	breast				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0764	NCI_CGAP_Co3	colon				pT7T3D-Pac (Pharmacia) with a modified

						polylinker
L0766	NCI_CGAP_GCB1	germinal center B cell				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0768	NCI_CGAP_GC4	pooled germ cell tumors				pT7T3D-Pac (Pharmacia) with a modified polylinker
L0769	NCI_CGAP_Brn25	anaplastic oligodendroglioma	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0770	NCI_CGAP_Brn23	glioblastoma (pooled)	brain			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0772	NCI_CGAP_Co10	colon tumor RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0773	NCI_CGAP_Co9	colon tumor RER+	colon			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0774	NCI_CGAP_Kid3		kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0775	NCI_CGAP_Kid5	2 pooled tumors (clear cell type)	kidney			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0776	NCI_CGAP_Lu5	carcinoid	lung			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0777	Soares_NhHMPu_S1	Pooled human melanocyte, fetal heart, and pregnant	mixed (see below)			pT7T3D-Pac (Pharmacia) with a modified polylinker
L0779	Soares_NFL_T_GBC_S1		pooled			pT7T3D-Pac

						(Pharmacia) with a modified polylinker
L0780	Soares_NSF_F8_9W_O T_PA_P_S1		pooled			pT7T3D- Pac (Pharmacia) with a modified polylinker
L0781	Barstead prostate BPH HPLRB4		prostate			pT7T3D- Pac (Pharmacia) with a modified polylinker
L0783	NCI_CGAP_Pr22	normal prostate	prostate			pT7T3D- Pac (Pharmacia) with a modified polylinker
L0789	NCI_CGAP_Sub3					pT7T3D- Pac (Pharmacia) with a modified polylinker
L0791	NCI_CGAP_Sub5					pT7T3D- Pac (Pharmacia) with a modified polylinker
L0792	NCI_CGAP_Sub6					pT7T3D- Pac (Pharmacia) with a modified polylinker
L0794	NCI_CGAP_GC6	pooled germ cell tumors				pT7T3D- Pac (Pharmacia) with a modified polylinker
L0800	NCI_CGAP_Co16	colon tumor, RER+	colon			pT7T3D- Pac (Pharmacia) with a modified polylinker
L0803	NCI_CGAP_Kid11		kidney			pT7T3D- Pac (Pharmacia) with a modified polylinker
L0804	NCI_CGAP_Kid12	2 pooled tumors (clear cell type)	kidney			pT7T3D- Pac (Pharmacia) with a modified

L0805	NCI_CGAP_Lu24	carcinoid	lung			polylinker pT7T3D- Pac (Pharmacia) with a modified polylinker
L0806	NCI_CGAP_Lu19	squamous cell carcinoma, poorly differentiated (4	lung			pT7T3D- Pac (Pharmacia) with a modified polylinker
L0809	NCI_CGAP_Pr28		prostate			pT7T3D- Pac (Pharmacia) with a modified polylinker
L2251	Human fetal lung	Fetal lung				

TABLE 5

OMIM Reference	Description
102200	Somatotrophinoma
106100	Angioedema, hereditary
107680	ApoA-I and apoC-III deficiency, combined
107680	Corneal clouding, autosomal recessive
107680	Amyloidosis, 3 or more types
107680	Hypertriglyceridemia, one form
107680	Hypoalphalipoproteinemia
107720	Hypertriglyceridemia
108725	Atherosclerosis, susceptibility to
120550	C1q deficiency, type A
120570	C1q deficiency, type B
120575	C1q deficiency, type C
120700	C3 deficiency
120950	C8 deficiency, type I
120960	C8 deficiency, type II
130500	Elliptocytosis-1
131100	Multiple endocrine neoplasia I
131100	Prolactinoma, hyperparathyroidism, carcinoid syndrome
131100	Carcinoid tumor of lung
133171	[Erythrocytosis, familial], 133100
133200	Erythrokeratoderma variabilis
133780	Vitreoretinopathy, exudative, familial
134934	Thanatophoric dysplasia, types I and II, 187600
134934	Achondroplasia, 100800

134934	Craniosynostosis, nonsyndromic
134934	Crouzon syndrome with acanthosis nigricans
134934	Hypochondroplasia, 146000
136836	Fucosyltransferase-6 deficiency
138140	Glucose transport defect, blood-brain barrier
143100	Huntington disease
145981	Hypocalciuric hypercalcemia, type II
147050	Atopy
147141	Leukemia, acute lymphoblastic
147791	Jacobsen syndrome
153454	Ehlers-Danlos syndrome, type VI, 225400
153700	Macular dystrophy, vitelliform type
159555	Leukemia, myeloid/lymphoid or mixed-lineage
161015	Mitochondrial complex I deficiency, 252010
164009	Leukemia, acute promyelocytic, NUPA/RARA type
164953	Liposarcoma
167410	Rhabdomyosarcoma, alveolar, 268220
168000	Paraganglioma, familial nonchromaffin, 1
168360	Paraneoplastic sensory neuropathy
168461	Multiple myeloma, 254250
168461	Parathyroid adenomatosis 1
168461	Centrocytic lymphoma
171760	Hypophosphatasia, adult, 146300
171760	Hypophosphatasia, infantile, 241500
176100	Porphyria cutanea tarda
176100	Porphyria, hepatoerythropoietic
177070	Spherocytosis, hereditary, Japanese type
177070	Hermansky-Pudlak syndrome, 203300
178300	Ptosis, hereditary congenital, 1
180072	Night blindness, congenital stationary, type 3, 163500
180072	Retinitis pigmentosa, autosomal recessive
180721	Retinitis pigmentosa, digenic
180840	Susceptibility to IDDM
182500	Cataract, congenital
186740	Immunodeficiency due to defect in CD3-gamma
186830	Immunodeficiency, T-cell receptor/CD3 complex
187040	Leukemia-1, T-cell acute lymphoblastic
188025	Thrombocytopenia, Paris-Trousseau type
188070	Bleeding disorder due to defective thromboxane A2 receptor
191181	Cervical carcinoma
193235	Vitreoretinopathy, neovascular inflammatory
194190	Wolf-Hirschhorn syndrome
203750	3-ketothiolase deficiency
209901	Bardet-Biedl syndrome 1
218000	Andermann syndrome

227220	[Eye color, brown]
230000	Fucosidosis
232600	McArdle disease
243500	Isovalericacidemia
252800	Mucopolysaccharidosis 1h
252800	Mucopolysaccharidosis 1h/s
252800	Mucopolysaccharidosis 1s
255800	Schwartz-Jampel syndrome
256700	Neuroblastoma
259700	Osteopetrosis, recessive
259770	Osteoporosis-pseudoglioma syndrome
261640	Phenylketonuria due to PTS deficiency
300011	Menkes disease, 309400
300011	Occipital horn syndrome, 304150
300011	Cutis laxa, neonatal
300127	Mental retardation, X-linked, 60
305450	FG syndrome
313700	Perineal hypospadias
313700	Prostate cancer
313700	Spinal and bulbar muscular atrophy of Kennedy, 313200
313700	Breast cancer, male, with Reifenstein syndrome
313700	Androgen insensitivity, several forms
600045	Xeroderma pigmentosum, group E, subtype 2
600048	Breast cancer-3
600101	Deafness, autosomal dominant 2
600319	Diabetes mellitus, insulin-dependent, 4
600528	CPT deficiency, hepatic, type I, 255120
600650	Myopathy due to CPT II deficiency, 255110
600650	CPT deficiency, hepatic, type II, 600649
600722	Ceroid lipofuscinosis, neuronal, variant juvenile type, with granular osmiophilic deposits
600722	Ceroid lipofuscinosis, neuronal-1, infantile, 256730
600839	Barter syndrome, 241200
600957	Persistent Mullerian duct syndrome, type I, 261550
600965	Deafness, autosomal dominant 6
600975	Glaucoma 3, primary infantile, B
601238	Cerebellar ataxia, Cayman type
601382	Charcot-Marie-Tooth neuropathy-4B
601800	[Hair color, brown]
601846	Muscular dystrophy with rimmed vacuoles
601884	[High bone mass]
602216	Peutz-Jeghers syndrome, 175200
602477	Febrile convulsions, familial, 2
602574	Deafness, autosomal dominant 12, 601842
602574	Deafness, autosomal dominant 8, 601543

Polynucleotide and Polypeptide Variants

[095] The present invention is also directed to variants of the connective tissue associated polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, nucleotide sequences encoding the polypeptide of SEQ ID NO:Y, the nucleotide sequence of SEQ ID NO:X encoding the polypeptide sequence as defined in column 6 of Table 1A, nucleotide sequences encoding the polypeptide as defined in column 6 of Table 1A, the nucleotide sequence as defined in columns 8 and 9 of Table 2, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, the nucleotide sequence as defined in column 6 of Table 1B, nucleotide sequences encoding the polypeptide encoded by the nucleotide sequence as defined in column 6 of Table 1B, the cDNA sequence contained in Clone ID NO:Z, and/or nucleotide sequences encoding a polypeptide encoded by the cDNA sequence contained in Clone ID NO:Z.

[096] The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y, a polypeptide sequence as defined in column 6 of Table 1A, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the nucleotide sequence as defined in columns 8 and 9 of Table 2, a polypeptide sequence encoded by the nucleotide sequence as defined in column 6 of Table 1B, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, and/or a polypeptide sequence encoded by the cDNA sequence contained in Clone ID NO:Z.

[097] "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

[098] Thus, one aspect of the invention provides an isolated nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide having a nucleotide sequence selected from the group consisting of: (a) a nucleotide sequence described in SEQ ID NO:X or contained in the cDNA sequence of Clone ID NO:Z; (b) a nucleotide sequence in SEQ ID NO:X or the cDNA in Clone ID NO:Z which encodes a mature connective tissue associated polypeptide; (c) a nucleotide sequence in SEQ ID NO:X or the cDNA

sequence of Clone ID NO:Z, which encodes a biologically active fragment of a connective tissue associated polypeptide; (d) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of Clone ID NO:Z, which encodes an antigenic fragment of a connective tissue associated polypeptide; (e) a nucleotide sequence encoding a connective tissue associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (f) a nucleotide sequence encoding a mature connective tissue associated polypeptide of the amino acid sequence of SEQ ID NO:Y or the amino acid sequence encoded by the cDNA in Clone ID NO:Z; (g) a nucleotide sequence encoding a biologically active fragment of a connective tissue associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (h) a nucleotide sequence encoding an antigenic fragment of a connective tissue associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; and (i) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), or (h), above.

[099] The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the cDNA contained in Clone ID NO:Z or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in Clone ID NO:Z, the nucleotide coding sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto, the nucleotide coding sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto, a nucleotide sequence encoding the polypeptide encoded

by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto, the nucleotide sequence in SEQ ID NO:X encoding the polypeptide sequence as defined in column 6 of Table 1A or the complementary strand thereto, nucleotide sequences encoding a polypeptide as defined in column 6 of Table 1A or the complementary strand thereto, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides and nucleic acids.

[0100] In a preferred embodiment, the invention encompasses nucleic acid molecules which comprise, or alternatively, consist of a polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under lower stringency conditions, to a polynucleotide in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above, as are polypeptides encoded by these polynucleotides. In another preferred embodiment, polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[0101] In another embodiment, the invention provides a purified protein comprising, or alternatively consisting of, a polypeptide having an amino acid sequence selected from the group consisting of: (a) the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; (b) the amino acid sequence of a mature connective tissue associated polypeptide having the amino acid sequence of SEQ ID NO:Y or the amino acid sequence encoded by the cDNA in Clone ID NO:Z; (c) the amino acid sequence of a biologically active fragment of a connective tissue associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z; and (d) the amino acid sequence of an antigenic fragment of a connective tissue associated polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Clone ID NO:Z.

[0102] The present invention is also directed to proteins which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the amino acid

sequences in (a), (b), (c), or (d), above, the amino acid sequence shown in SEQ ID NO:Y, the amino acid sequence encoded by the cDNA contained in Clone ID NO:Z, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X as defined in columns 8 and 9 of Table 2, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B, the amino acid sequence as defined in column 6 of Table 1A, an amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X, and an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X. Fragments of these polypeptides are also provided (e.g., those fragments described herein). Further proteins encoded by polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these amino acid sequences under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are the polynucleotides encoding these proteins.

[0103] By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence referred to in Table 1A or 2 as the ORF (open reading frame), or any fragment specified, as described herein.

[0104] As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a sequence alignment the query and subject sequences are both DNA

sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

[0105] If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

[0106] For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected.

Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

[0107] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[0108] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence of a polypeptide referred to in Table 1A (e.g., an amino acid sequence identified in columns 5 or 6) or Table 2 (e.g., the amino acid sequence of the polypeptide encoded by the polynucleotide sequence defined in columns 8 and 9 of Table 2) or a fragment thereof, the amino acid sequence of the polypeptide encoded by the polynucleotide sequence in SEQ ID NO:B as defined in column 6 of Table 1B or a fragment thereof, the amino acid sequence of the polypeptide encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or an amino acid sequence of the polypeptide encoded by cDNA contained in Clone ID NO:Z, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237-245 (1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is expressed as percent identity. Preferred parameters used in a

FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

[0109] If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

[0110] For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue

positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

[0111] The polynucleotide variants of the invention may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations, which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, polypeptide variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

[0112] Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

[0113] Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptides of the present invention without substantial loss of biological function. As an example, the authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

[0114] Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem. 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

[0115] Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0116] Thus, the invention further includes polypeptide variants which show a functional activity (e.g., biological activity) of the polypeptides of the invention. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

[0117] The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, (e.g., encoding a polypeptide having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having functional activity include, *inter alia*, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in

situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); (3) Northern Blot analysis for detecting mRNA expression in specific tissues (e.g., normal connective tissues or diseased connective tissues); and (4) *in situ* hybridization (e.g., histochemistry) for detecting mRNA expression in specific tissues (e.g., normal connective tissue or diseased connective tissues).

[0118] Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having functional activity. By a polypeptide having "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide of the invention for binding) to an anti-polypeptide of the invention antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

[0119] The functional activity of the polypeptides, and fragments, variants and derivatives of the invention, can be assayed by various methods.

[0120] For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the present invention for binding to an anti-polypeptide of the invention antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, *in situ* immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding

of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

[0121] In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, the ability of physiological correlates of a polypeptide of the present invention to bind to a substrate(s) of the polypeptide of the invention can be routinely assayed using techniques known in the art.

[0122] In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants and derivatives thereof to elicit polypeptide related biological activity (either *in vitro* or *in vivo*). Other methods will be known to the skilled artisan and are within the scope of the invention.

[0123] Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA contained in Clone ID NO:Z, a nucleic acid sequence referred to in Table 1A (e.g., SEQ ID NO:X), a nucleic acid sequence disclosed in Table 2 (e.g., the nucleic acid sequence delineated in columns 8 and 9) or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

[0124] For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

[0125] The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

[0126] The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. See Cunningham et al., Science 244:1081-1085 (1989). The resulting mutant molecules can then be tested for biological activity.

[0127] As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitutions, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or

(ii) substitutions with one or more of the amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, serum albumin (preferably human serum albumin) or a fragment or variant thereof, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

[0128] For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. See Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).

[0129] A further embodiment of the invention relates to polypeptides which comprise the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions from a polypeptide sequence disclosed herein. Of course it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, an amino acid sequence encoded by the complement of SEQ ID NO:X, and/or the amino acid sequence encoded by cDNA contained in Clone ID NO:Z which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions.

[0130] In specific embodiments, the polypeptides of the invention comprise, or alternatively, consist of, fragments or variants of a reference amino acid sequence selected from: (a) the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature form and/or other fragments described herein); (b) the amino acid sequence

encoded by SEQ ID NO:X or fragments thereof; (c) the amino acid sequence encoded by the complement of SEQ ID NO:X or fragments thereof; (d) the amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or fragments thereof; and (e) the amino acid sequence encoded by cDNA contained in Clone ID NO:Z or fragments thereof; wherein the fragments or variants have 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, amino acid residue additions, substitutions, and/or deletions when compared to the reference amino acid sequence. In preferred embodiments, the amino acid substitutions are conservative. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Polynucleotide and Polypeptide Fragments

[0131] The present invention is also directed to polynucleotide fragments of the polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers to a polynucleotide having a nucleic acid sequence which, for example: is a portion of the cDNA contained in Clone ID NO:Z or the complementary strand thereto; is a portion of the polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in Clone ID NO:Z or the complementary strand thereto; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence of SEQ ID NO:X as defined in columns 8 and 9 of Table 2 or the complementary strand thereto; is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X; is a polynucleotide sequence encoding a portion of a polypeptide encoded by the complement of the polynucleotide sequence in SEQ ID NO:X; is a portion of a polynucleotide sequence encoding the amino acid sequence encoded by the region of SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto; or is a portion of the polynucleotide sequence of SEQ ID NO:B as defined in column 6 of Table 1B or the complementary strand thereto.

[0132] The polynucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and

even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in Clone ID NO:Z, or the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 160, 170, 180, 190, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

[0133] Moreover, representative examples of polynucleotide fragments of the invention, comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or

7301 to the end of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide, which has a functional activity (e.g., biological activity). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[0134] Further representative examples of polynucleotide fragments of the invention, comprise, or alternatively consist of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, 6151-6200, 6201-6250, 6251-6300, 6301-6350, 6351-6400, 6401-6450, 6451-6500, 6501-6550, 6551-6600, 6601-6650, 6651-6700, 6701-6750, 6751-6800, 6801-6850, 6851-6900, 6901-6950, 6951-7000, 7001-7050, 7051-7100, 7101-7150, 7151-7200, 7201-7250, 7251-7300 or 7301 to the end of the cDNA sequence contained in Clone ID NO:Z, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller

by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide, which has a functional activity (e.g., biological activity). More preferably, these polynucleotides can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[0135] Moreover, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence delineated in Table 1B column 6. Additional, representative examples of polynucleotide fragments of the invention comprise, or alternatively consist of, a nucleic acid sequence comprising one, two, three, four, five, six, seven, eight, nine, ten, or more of the above described polynucleotide fragments of the invention in combination with a polynucleotide sequence that is the complementary strand of a sequence delineated in column 6 of Table 1B. In further embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that of the BAC fragment having the sequence disclosed in SEQ ID NO:B (see Table 1B, column 5). In additional embodiments, the above-described polynucleotide fragments of the invention comprise, or alternatively consist of, sequences delineated in Table 1B, column 6, and have a nucleic acid sequence which is different from that published for the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). In additional embodiments, the above-described polynucleotides of the invention comprise, or alternatively consist of, sequences delineated Table 1B, column 6, and have a nucleic acid sequence which is different from that contained in the BAC clone identified as BAC ID NO:A (see Table 1B, column 4). Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides and polypeptides are also encompassed by the invention.

[0136] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1B, column 2) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0137] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in column 6 of Table 1B which correspond to the same Clone ID NO:Z (see Table 1B, column 1), and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0138] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, or more fragments of the sequences delineated in the same row of column 6 of Table 1B, and the polynucleotide sequence of SEQ ID NO:X (e.g., as defined in Table 1A or 1B) or fragments or variants thereof. Polypeptides encoded by these polynucleotides, other polynucleotides that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention.

[0139] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of the sequence of SEQ ID NO:X are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids that encode these polypeptides, and antibodies that bind these polypeptides are also encompassed by the

invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0140] In additional specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X (e.g., as described herein) are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0141] In further specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of a fragment or variant of the sequence of SEQ ID NO:X and the 5' 10 polynucleotides of the sequence of one of the sequences delineated in column 6 of Table 1B are directly contiguous. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0142] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of a polynucleotide sequence in which the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B and the 5' 10 polynucleotides of another sequence in column 6 are directly contiguous. In preferred embodiments, the 3' 10 polynucleotides of one of the sequences delineated in column 6 of Table 1B is directly contiguous with the 5' 10 polynucleotides of the next sequential exon delineated in Table

1B, column 6. Nucleic acids which hybridize to the complement of these 20 contiguous polynucleotides under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention. Polypeptides encoded by these polynucleotides and/or nucleic acids, other polynucleotides and/or nucleic acids encoding these polypeptides, and antibodies that bind these polypeptides are also encompassed by the invention. Additionally, fragments and variants of the above-described polynucleotides, nucleic acids, and polypeptides are also encompassed by the invention.

[0143] In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y, a portion of an amino acid sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, a portion of an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, and/or a portion of an amino acid sequence encoded by the cDNA contained in Clone ID NO:Z. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region. In a preferred embodiment, polypeptide fragments of the invention include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-

460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, or 1441 to the end of the coding region of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

[0144] Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[0145] Accordingly, polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the

carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions is preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

[0146] The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X or the complement thereof, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, a polypeptide encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1B, and/or a polypeptide encoded by the cDNA contained in Clone ID NO:Z). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y, or the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0147] The present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, a polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or a polypeptide encoded by the cDNA contained in Clone ID NO:Z). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where n corresponds to the position of amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0148] In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y and the polypeptide encoded by the portion of

SEQ ID NO:X as defined in columns 8 and 9 of Table 2), the cDNA contained in Clone ID NO:Z, and/or the complement thereof, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0149] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[0150] The present application is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0151] Any polypeptide sequence encoded by, for example, the polynucleotide sequences set forth as SEQ ID NO:X or the complement thereof, (presented, for example, in Tables 1A and 2), the cDNA contained in Clone ID NO:Z, or the polynucleotide sequence as defined in column 6 of Table 1B, may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polynucleotide sequence of SEQ ID NO:X (e.g., the polypeptide of SEQ ID NO:Y and the polypeptide encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2) or the cDNA contained in Clone ID NO:Z may be analyzed using the default parameters of the DNASTAR computer

algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; <http://www.dnastar.com/>).

[0152] Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman alpha-regions, beta-regions, and turn-regions; Kyte-Doolittle hydrophilic regions and hydrophobic regions; Eisenberg alpha- and beta-amphipathic regions; Karplus-Schulz flexible regions; Emini surface-forming regions; and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

[0153] Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[0154] Preferred polypeptide fragments of the invention are fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a functional activity (e.g. biological activity) of the polypeptide sequence of which the amino acid sequence is a fragment. By a polypeptide displaying a "functional activity" is meant a polypeptide capable of one or more known functional activities associated with a full-length protein, such as, for example, biological activity, antigenicity, immunogenicity, and/or multimerization, as described herein.

[0155] Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[0156] In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0157] The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of: the polypeptide sequence shown in SEQ ID NO:Y; a polypeptide sequence encoded by SEQ ID NO:X or the complementary strand thereto; the polypeptide sequence encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2; the polypeptide sequence encoded by the portion of SEQ ID NO:B as defined in column 6 of Table 1B or the complement thereto; the polypeptide sequence encoded by the cDNA contained in Clone ID NO:Z; or the polypeptide sequence encoded by a polynucleotide that hybridizes to the sequence of SEQ ID NO:X, the complement of the sequence of SEQ ID NO:X, the complement of a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, or the cDNA sequence contained in Clone ID NO:Z under stringent hybridization conditions or alternatively, under lower stringency hybridization as defined *supra*. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X, or a fragment thereof), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions defined *supra*.

[0158] The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described *infra*. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well

known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross-reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

[0159] Fragments, which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

[0160] In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

[0161] Non-limiting examples of epitopes of polypeptides that can be used to generate antibodies of the invention include a polypeptide comprising, or alternatively consisting of, at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y specified in column 6 of Table 1A. These polypeptide fragments have been determined to bear antigenic epitopes of the proteins of the invention by the analysis of the Jameson-Wolf antigenic index, which is included in the DNASTar suite of computer programs. By "comprise" it is intended that a polypeptide contains at least one, two, three, four, five, six or more of the portion(s) of SEQ ID NO:Y shown in column 6 of Table 1A, but it may contain additional flanking residues on either the amino or carboxyl termini of the recited portion. Such additional flanking sequences are preferably sequences naturally found adjacent to the portion; i.e., contiguous sequence shown in SEQ ID NO:Y. The flanking sequence may, however, be sequences from a heterologous

polypeptide, such as from another protein described herein or from a heterologous polypeptide not described herein. In particular embodiments, epitope portions of a polypeptide of the invention comprise one, two, three, or more of the portions of SEQ ID NO:Y shown in column 6 of Table 1A. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0162] Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. See, for instance, Sutcliffe et al., *supra*; Wilson et al., *supra*; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[0163] Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, *in vivo* immunization, *in vitro* immunization, and phage display methods. See, e.g., Sutcliffe et al., *supra*; Wilson et al., *supra*, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If *in vivo* immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster

injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

[0164] As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention (e.g., those comprising an immunogenic or antigenic epitope) can be fused to heterologous polypeptide sequences. For example, polypeptides of the present invention (including fragments or variants thereof), may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof, resulting in chimeric polypeptides. By way of another non-limiting example, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused with albumin (including but not limited to recombinant human serum albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). In a preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with the mature form of human serum albumin (i.e., amino acids 1 – 585 of human serum albumin as shown in Figures 1 and 2 of EP Patent 0 322 094) which is herein incorporated by reference in its entirety. In another preferred embodiment, polypeptides and/or antibodies of the present invention (including fragments or variants thereof) are fused with polypeptide fragments comprising, or alternatively consisting of, amino acid residues 1-z of human serum albumin, where z is an integer from 369 to 419, as described in U.S. Patent 5,766,883 herein incorporated by reference in its entirety. Polypeptides and/or antibodies of the present invention (including fragments or variants thereof) may be fused to either the N- or C-terminal end of the heterologous protein (e.g., immunoglobulin Fc polypeptide or human serum albumin polypeptide). Polynucleotides encoding fusion proteins of the invention are also encompassed by the invention.

[0165] Such fusion proteins as those described above may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins consisting of

the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion desulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin (HA) tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni²⁺ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

Fusion Proteins

[0166] Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

[0167] Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous

functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

[0168] In certain preferred embodiments, proteins of the invention are fusion proteins comprising an amino acid sequence that is an N and/or C- terminal deletion of a polypeptide of the invention. In preferred embodiments, the invention is directed to a fusion protein comprising an amino acid sequence that is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence of the invention. Polynucleotides encoding these proteins are also encompassed by the invention.

[0169] Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides is familiar and routine techniques in the art.

[0170] As one of skill in the art will appreciate that, as discussed above, polypeptides of the present invention, and epitope-bearing fragments thereof, can be combined with heterologous polypeptide sequences. For example, the polypeptides of the present invention may be fused with heterologous polypeptide sequences, for example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), or albumin (including, but not limited to, native or recombinant human albumin or fragments or variants thereof (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)), resulting in chimeric polypeptides. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties (EP-A 0232 262). Alternatively, deleting the Fc part after the fusion protein

has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. See, D. Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); K. Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995).

[0171] Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a polypeptide, which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., *Cell* 37:767 (1984).)

[0172] Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"), briefly described below, and further described herein. DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, *Trends Biotechnol.* 16(2):76-82 (1998); Hansson et al., *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo and Blasco, *Biotechniques* 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference in its entirety). In a preferred embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc., of one or more heterologous molecules encoding a heterologous polypeptide.

[0173] Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

Recombinant and Synthetic Production of Polypeptides of the Invention

[0174] The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by synthetic and recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

[0175] The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged *in vitro* using an appropriate packaging cell line and then transduced into host cells.

[0176] The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli lac*, *trp*, *phoA* and *tac* promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

[0177] As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance, glutamine synthase, for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, 293, NSO and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

[0178] Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

[0179] Vectors which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulphoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors is the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657 which are hereby incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors can be obtained from Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington *et al.*, *Bio/technology* 10:169(1992) and in Biblia and Robinson *Biotechnol. Prog.* 11:1 (1995) which are herein incorporated by reference.

[0180] The present invention also relates to host cells containing the above-described vector constructs described herein, and additionally encompasses host cells containing nucleotide sequences of the invention that are operably associated with one or more heterologous control regions (e.g., promoter and/or enhancer) using techniques known of in the art. The host cell can be a higher eukaryotic cell, such as a mammalian cell (e.g., a human derived cell), or a lower eukaryotic cell, such as a yeast cell, or the host cell can be

a prokaryotic cell, such as a bacterial cell. A host strain may be chosen, which modulates the expression of the inserted gene sequences, or modifies and processes the gene product in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically engineered polypeptide may be controlled. Furthermore, different host cells have characteristics and specific mechanisms for the translational and post-translational processing and modification (e.g., phosphorylation, cleavage) of proteins. Appropriate cell lines can be chosen to ensure the desired modifications and processing of the foreign protein expressed.

[0181] Introduction of the nucleic acids and nucleic acid constructs of the invention into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., *Basic Methods In Molecular Biology* (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

[0182] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., connective tissue antigen coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with connective tissue associated polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous connective tissue associated polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous connective tissue associated polynucleotide sequences via homologous recombination (see, e.g., US Patent Number 5,641,670, issued June 24, 1997; International Publication Number WO 96/29411; International Publication Number WO 94/12650; Koller *et al.*, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); and Zijlstra *et al.*, *Nature* 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[0183] Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly

isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

[0184] In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolism pathway is the oxidation of methanol to formaldehyde using O₂. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O₂. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See, Ellis, S.B., *et al.*, *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., *et al.*, *Yeast* 5:167-77 (1989); Tschopp, J.F., *et al.*, *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

[0185] In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J.

Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

[0186] Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

[0187] In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

[0188] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[0189] In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and

Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, α -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0190] The invention encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH_4 ; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

[0191] Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

[0192] Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable

fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include iodine (^{121}I , ^{123}I , ^{125}I , ^{131}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{111}In , ^{112}In , $^{113\text{m}}\text{In}$, $^{115\text{m}}\text{In}$), technetium (^{99}Tc , $^{99\text{m}}\text{Tc}$), thallium (^{201}Tl), gallium (^{68}Ga , ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , and ^{97}Ru .

[0193] In specific embodiments, a polypeptide of the present invention or fragment or variant thereof is attached to macrocyclic chelators that associate with radiometal ions, including but not limited to, ^{177}Lu , ^{90}Y , ^{166}Ho , and ^{153}Sm , to polypeptides. In a preferred embodiment, the radiometal ion associated with the macrocyclic chelators is ^{111}In . In another preferred embodiment, the radiometal ion associated with the macrocyclic chelator is ^{90}Y . In specific embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA). In other specific embodiments, DOTA is attached to an antibody of the invention or fragment thereof via a linker molecule. Examples of linker molecules useful for conjugating DOTA to a polypeptide are commonly known in the art - see, for example, DeNardo et al., Clin Cancer Res. 4(10):2483-90 (1998); Peterson et al., Bioconjug. Chem. 10(4):553-7 (1999); and Zimmerman et al., Nucl. Med. Biol. 26(8):943-50 (1999); which are hereby incorporated by reference in their entirety.

[0194] As mentioned, the connective tissue associated proteins of the invention may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given connective tissue associated polypeptide. Connective tissue associated polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic connective tissue associated polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide

derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth. Enzymol. 182:626-646 (1990); Rattan et al., Ann. N.Y. Acad. Sci. 663:48-62 (1992)).

[0195] Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0196] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200, 500, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 8500, 9000, 9500, 10,000, 10,500, 11,000, 11,500, 12,000, 12,500, 13,000, 13,500,

14,000, 14,500, 15,000, 15,500, 16,000, 16,500, 17,000, 17,500, 18,000, 18,500, 19,000, 19,500, 20,000, 25,000, 30,000, 35,000, 40,000, 50,000, 55,000, 60,000, 65,000, 70,000, 75,000, 80,000, 85,000, 90,000, 95,000, or 100,000 kDa.

[0197] As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo et al., *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev et al., *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti et al., *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[0198] The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, such as, for example, the method disclosed in EP 0 401 384 (coupling PEG to G-CSF), herein incorporated by reference; see also Malik et al., *Exp. Hematol.* 20:1028-1035 (1992), reporting pegylation of GM-CSF using tresyl chloride. For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0199] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

[0200] One may specifically desire proteins chemically modified at the N-terminus.

Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[0201] As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992); Francis et al., Intern. J. of Hematol. 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

[0202] One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($\text{ClSO}_2\text{CH}_2\text{CF}_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

[0203] Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates

wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number of additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in International Publication No. WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

[0204] The number of polyethylene glycol moieties attached to each protein of the invention (i.e., the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado et al., Crit. Rev. Thera. Drug Carrier Sys. 9:249-304 (1992).

[0205] The connective tissue associated polypeptides of the invention can be recovered and purified from chemical synthesis and recombinant cell cultures by standard methods which include, but are not limited to, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification. Well known techniques for refolding protein may be employed to regenerate active conformation when the polypeptide is denatured during isolation and/or purification.

[0206] Connective tissue associated polynucleotides and polypeptides may be used in accordance with the present invention for a variety of applications, particularly those that make use of the chemical and biological properties of connective tissue associated antigens. Among these are applications in the detection, prevention, diagnosis and/or treatment of diseases associated with connective tissues, such as e.g., cancer, tumors,

having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing two polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing three polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

[0210] As used herein, the term heteromer refers to a multimer containing two or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

[0211] Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked by, for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, encoded by the portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or encoded by the cDNA contained in Clone ID NO:Z). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation.

Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., U.S. Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

[0212] Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

[0213] Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994))

and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

[0214] In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

[0215] The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

[0216] Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding

a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., U.S. Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Antibodies

[0217] Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of the invention (e.g., a polypeptide or fragment or variant of the amino acid sequence of SEQ ID NO:Y or a polypeptide encoded by the cDNA contained in Clone ID NO:Z, and/or an epitope, of the present invention) as determined by immunoassays well known in the art for assaying specific antibody-antigen binding. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), intracellularly-made antibodies (i.e., intrabodies), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule. In preferred embodiments, the immunoglobulin molecules of the invention are IgG1. In other preferred embodiments, the immunoglobulin molecules of the invention are IgG4.

[0218] Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')₂, Fd,

single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, sheep rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described *infra* and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

[0219] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

[0220] Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues, or listed in the Tables and Figures. Preferred epitopes of the invention include those shown in column 6 of Table 1A, as well as polynucleotides that encode these epitopes. Antibodies, which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

[0223] Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies, which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described *supra*). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

[0224] The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies, which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-

247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

[0225] Antibodies of the present invention may be used, for example, to purify, detect, and target the polypeptides of the present invention, including both *in vitro* and *in vivo* diagnostic and therapeutic methods. For example, the antibodies have utility in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); incorporated by reference herein in its entirety.

[0226] As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalent and non-covalent conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387; the disclosures of which are incorporated herein by reference in their entireties.

[0227] The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[0231] Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

[0232] Another well known method for producing both polyclonal and monoclonal human B cell lines is transformation using Epstein Barr Virus (EBV). Protocols for generating EBV-transformed B cell lines are commonly known in the art, such as, for example, the protocol outlined in Chapter 7.22 of Current Protocols in Immunology, Coligan et al., Eds., 1994, John Wiley & Sons, NY, which is hereby incorporated in its entirety by reference herein. The source of B cells for transformation is commonly human peripheral blood, but B cells for transformation may also be derived from other sources including, but not limited to, lymph nodes, tonsil, spleen, tumor tissue, and infected tissues. Tissues are generally made into single cell suspensions prior to EBV transformation. Additionally, steps may be taken to either physically remove or inactivate T cells (e.g., by treatment with cyclosporin A) in B cell-containing samples, because T cells from individuals seropositive for anti-EBV antibodies can suppress B cell immortalization by EBV.

[0233] In general, the sample containing human B cells is inoculated with EBV, and cultured for 3-4 weeks. A typical source of EBV is the culture supernatant of the B95-8 cell line (ATCC #VR-1492). Physical signs of EBV transformation can generally be seen towards the end of the 3-4 week culture period. By phase-contrast microscopy, transformed cells may appear large, clear, hairy and tend to aggregate in tight clusters of cells. Initially, EBV lines are generally polyclonal. However, over prolonged periods of cell cultures, EBV lines may become monoclonal or polyclonal as a result of the selective outgrowth of particular B cell clones. Alternatively, polyclonal EBV transformed lines may be subcloned (e.g., by limiting dilution culture) or fused with a suitable fusion

partner and plated at limiting dilution to obtain monoclonal B cell lines. Suitable fusion partners for EBV transformed cell lines include mouse myeloma cell lines (e.g., SP2/0, X63-Ag8.653), heteromyeloma cell lines (human x mouse; e.g., SPAM-8, SBC-H20, and CB-F7), and human cell lines (e.g., GM 1500, SKO-007, RPMI 8226, and KR-4). Thus, the present invention also provides a method of generating polyclonal or monoclonal human antibodies against polypeptides of the invention or fragments thereof, comprising EBV-transformation of human B cells.

[0234] Antibody fragments, which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')₂ fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). F(ab')₂ fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain. For example, the antibodies of the present invention can also be generated using various phage display methods known in the art and as discussed in detail in the Examples (e.g., Example 10). In phage display methods, functional antibody domains are displayed on the surface of phage particles, which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225;

5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0235] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')₂ fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

[0236] Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including *in vivo* use of antibodies in humans and *in vitro* detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and

sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

[0237] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

[0238] Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring, which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology.

The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; 5,939,598; 6,075,181 and 6,114,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0239] Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., *Bio/technology* 12:899-903 (1988)).

[0240] Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, *FASEB J.* 7(5):437-444; (1989) and Nissinoff, *J. Immunol.* 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand/receptor. For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby block its biological activity. Alternatively, antibodies which bind to and enhance polypeptide multimerization and/or binding, and/or receptor/ligand multimerization,

binding and/or signaling can be used to generate anti-idiotypes that function as agonists of a polypeptide of the invention and/or its ligand/receptor. Such agonistic anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens as agonists of the polypeptides of the invention or its ligand(s)/receptor(s). For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligand(s)/receptor(s), and thereby promote or enhance its biological activity.

- [0241] Intrabodies of the invention can be produced using methods known in the art, such as those disclosed and reviewed in Chen et al., Hum. Gene Ther. 5:595-601 (1994); Marasco, W.A., Gene Ther. 4:11-15 (1997); Rondon and Marasco, Annu. Rev. Microbiol. 51:257-283 (1997); Proba et al., J. Mol. Biol. 275:245-253 (1998); Cohen et al., Oncogene 17:2445-2456 (1998); Ohage and Steipe, J. Mol. Biol. 291:1119-1128 (1999); Ohage et al., J. Mol. Biol. 291:1129-1134 (1999); Wirtz and Steipe, Protein Sci. 8:2245-2250 (1999); Zhu et al., J. Immunol. Methods 231:207-222 (1999); and references cited therein.

Polynucleotides Encoding Antibodies

- [0242] The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined *supra*, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y, to a polypeptide encoded by a portion of SEQ ID NO:X as defined in columns 8 and 9 of Table 2, and/or to a polypeptide encoded by the cDNA contained in Clone ID NO:Z.

- [0243] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody,

annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0244] Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[0245] Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[0246] In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described *supra*. The framework regions may be naturally occurring or

consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed *supra*, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

[0247] In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described *supra*, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

[0248] Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in *E. coli* may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

Methods of Producing Antibodies

[0249] The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques. Methods of producing antibodies include, but are not

limited to, hybridoma technology, EBV transformation, and other methods discussed herein as well as through the use recombinant DNA technology, as discussed below.

[0250] Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

[0251] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0252] A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990)).

[0253] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a

fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0254] In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[0255] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by *in vitro* or *in vivo* recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

[0256] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage)

of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

[0257] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines, which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines, which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

[0258] A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)). genes can be employed in tk-, hgp^rt- or ap^rt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance

to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); TIB TECH 11(5):155-215 (1993); and hygromycin, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

[0259] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

[0260] Vectors, which use glutamine synthase (GS) or DHFR as the selectable markers can be amplified in the presence of the drugs methionine sulfoximine or methotrexate, respectively. An advantage of glutamine synthase based vectors are the availability of cell lines (e.g., the murine myeloma cell line, NS0) which are glutamine synthase negative. Glutamine synthase expression systems can also function in glutamine synthase expressing cells (e.g., Chinese Hamster Ovary (CHO) cells) by providing additional inhibitor to prevent the functioning of the endogenous gene. A glutamine synthase expression system and components thereof are detailed in PCT publications: WO87/04462; WO86/05807; WO89/01036; WO89/10404; and WO91/06657, which are incorporated in their entireties by reference herein. Additionally, glutamine synthase expression vectors that may be used according to the present invention are commercially

available from suppliers, including, for example Lonza Biologics, Inc. (Portsmouth, NH). Expression and production of monoclonal antibodies using a GS expression system in murine myeloma cells is described in Bebbington et al., Bio/technology 10:169(1992) and in Biblia and Robinson Biotechnol. Prog. 11:1 (1995) which are incorporated in their entirety by reference herein.

[0261] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers, which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0262] Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

[0263] The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either *in vitro* or *in vivo*, by

fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in *in vitro* immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., *supra*, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452 (1991), which are incorporated by reference in their entireties.

[0264] The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341 (1992) (said references incorporated by reference in their entireties).

[0265] As discussed, *supra*, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the *in vivo* half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See EP 394,827; Traunecker

et al., *Nature* 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide-linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. See, for example, Fountoulakis et al., *J. Biochem.* 270:3958-3964 (1995). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. See, for example, EP A 232,262. Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995)).

[0266] Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., *Cell* 37:767 (1984)) and the "flag" tag.

[0267] The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic

metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention.

[0268] Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ²¹³Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0269] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, α -interferon, β -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- α , TNF- β , AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (See, International Publication No. WO

99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[0270] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[0271] Techniques for conjugating such therapeutic moiety to antibodies are well known. See, for example, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

[0272] Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[0273] An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Immunophenotyping

[0274] The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. Translation products of the genes of the present invention may be useful as cell specific markers, or more specifically as cellular markers

that are differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison et al., Cell, 96:737-49 (1999)).

- [0275] These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

- [0276] The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, and protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

- [0277] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA,

PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al., eds., (1994), *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York, section 10.16.1.

[0278] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., ³²P or ¹²⁵I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al., eds., (1994), *Current Protocols in Molecular Biology*, Vol. 1, John Wiley & Sons, Inc., New York, section 10.8.1.

[0279] ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a

detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al., eds, (1994), Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, section 11.2.1.

[0280] The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of increasing amounts of an unlabeled second antibody.

[0281] Antibodies of the invention may be characterized using immunocytochemistry methods on cells (e.g., mammalian cells, such as CHO cells) transfected with a vector enabling the expression of a connective tissue antigen or with vector alone using techniques commonly known in the art. Antibodies that bind connective tissue antigen transfected cells, but not vector-only transfected cells, are connective tissue antigen specific.

Therapeutic Uses

[0282] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not

limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0283] In a specific and preferred embodiment, the present invention is directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the diseases, disorders, or conditions of connective tissues, including, but not limited to, rheumatoid arthritis, psoriatic arthritis, discoid lupus erythematosus, systemic lupus erythematosus, scleroderma, CREST syndrome, Sjogren's syndrome, polymyositis, dermatomyositis, mixed connective tissue disease, relapsing polychondritis, vasculitis, Henoch-Schonlein syndrome, erythema nodosum, polyarteritis nodosa, temporal (giant cell) arteritis, Takayasu's arteritis, Wegener's granulomatosis, Reiter's syndrome, Behcet's syndrome, ankylosing spondylitis, cellulitis, keloids, Ehler Danlos syndrome, Marfan syndrome, pseudoxantoma elasticum, osteogenesis imperfecta, chondrodysplasias, epidermolysis bullosa, Alport syndrome, cutis laxa, genetic disorders affecting skeleton, skin and muscles; formation of excessive scar tissue; deposition of pathological amounts of connective tissue in body organs, including kidney, intestines and heart, and in liver by liver cirrhosis, in skin by scleroderma, in lung by lung fibrosis, in bone marrow by leukemia, in blood vessels by atherosclerosis, and in joints by rheumatic diseases. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (e.g., antibodies directed to the full length protein expressed on the cell surface of a mammalian cell; antibodies directed to an epitope of a connective tissue associated polypeptide of the invention (such as, a linear epitope (shown in Table 1A, column 6) or a

conformational epitope), including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions of connective tissues described herein. The treatment and/or prevention of diseases, disorders, or conditions of connective tissues associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0284] A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[0285] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[0286] The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

[0287] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or K_d less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, and 10^{-15} M.

Gene Therapy

[0288] In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[0289] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[0290] For general reviews of the methods of gene therapy, see Goldspiel et al., Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

[0291] In a preferred embodiment, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that

express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

[0292] Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids *in vitro*, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or *ex vivo* gene therapy.

[0293] In a specific embodiment, the nucleic acid sequences are directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor

(see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

[0294] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., Biotherapy 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., J. Clin. Invest. 93:644-651 (1994); Kiem et al., Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

[0295] Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143-155 (1992); Mastrangeli et al., J. Clin. Invest. 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., Gene Therapy 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

[0296] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

[0297] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

[0298] In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

[0299] The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

[0300] Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular

hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

[0301] In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

[0302] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered *in vivo* for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained *in vitro* can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

[0303] In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by the presence or absence of an appropriate inducer of transcription.

Demonstration of Therapeutic or Prophylactic Activity

[0304] The compounds or pharmaceutical compositions of the invention are preferably tested *in vitro*, and then *in vivo* for the desired therapeutic or prophylactic activity, prior to use in humans. For example, *in vitro* assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, *in vitro* assays which can be used to determine whether administration of a specific compound is indicated, include *in vitro* cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

[0305] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred embodiment, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

[0306] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

[0307] Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0308] In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during

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surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[0309] In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

[0310] In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., *Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); see also Levy et al., *Science* 228:190 (1985); During et al., *Ann. Neurol.* 25:351 (1989); Howard et al., *J. Neurosurg.* 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, e.g., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115-138 (1984)).

[0311] Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

[0312] In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or

cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0313] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

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[0314] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0315] The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0316] The amount of the compound of the invention, which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, *in vitro* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0317] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the

immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

- [0318] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Diagnosis and Imaging

- [0319] Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

- [0320] The invention provides a diagnostic assay for diagnosing a connective tissue disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical

symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0321] Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0322] One facet of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. A preferred embodiment of the invention is the detection and diagnosis of a disease or disorder of connective tissues associated with aberrant expression of a connective tissue antigen in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[0323] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic

images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0324] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0325] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disorder, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[0326] Presence of the labeled molecule can be detected in the patient using methods known in the art for *in vivo* scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0327] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Kits

[0328] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

[0329] In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope, which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine, which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

[0330] In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

[0331] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the

polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[0332] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme, which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

[0333] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

[0334] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Uses of the Polynucleotides

[0335] Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

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[0336] The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art. Table 1A, column 8 provides the chromosome location of some of the polynucleotides of the invention.

[0337] Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

[0338] Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

[0339] Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

[0340] For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

[0341] Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 1A and/or Table 2 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

[0342] The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999), each of which is hereby incorporated by reference in its entirety.

[0343] Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library).) Column 9 of Table 1A provides an OMIM reference identification number of diseases associated with the cytologic band disclosed in column 8 of Table 1A, as determined using techniques described herein and by reference to Table 5. Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

[0344] Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicate that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the

mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

[0345] Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker. Diagnostic and prognostic methods, kits and reagents encompassed by the present invention are briefly described below and more thoroughly elsewhere herein (see e.g., the sections labeled "Antibodies", "Diagnostic Assays", and "Methods for Detecting Disease of Connective Tissue, Including Cancer").

[0346] Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder. Additional non-limiting examples of diagnostic methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., Example 12).

[0347] In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject, as further described herein. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31' mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

[0348] Where a diagnosis of a related disorder, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

described in U.S. Patents 5,858,659 and 5,856,104. The U.S. Patents referenced *supra* are hereby incorporated by reference in their entirety herein.

[0352] The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by Nielsen et al., *Science* 254:1497 (1991); and Egholm et al., *Nature* 365:666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point ($T_{sub.m}$) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

[0353] The compounds of the present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[0354] The compounds of the present invention have preferred uses which include, but are not limited to, detecting cancer of a connective tissue in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias, for example in detecting changes in the neosynthesis of collagens that is indicative or suggestive of the malignant state of cells derived from such tumors as breast cancer. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[0355] Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Germann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Germann et al., *supra*) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Germann et al., *supra*) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Germann et al., *supra*)

[0356] For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not be limited to treatment, prevention, diagnosis and/or prognosis, of proliferative disorders of cells and tissues of hematopoietic origin, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes. In preferred embodiments,

the compounds and/or methods of the invention are used to treat, prevent, diagnose, and/or prognose, proliferative disorders of connective tissue cells and tissues.

[0357] In addition to the foregoing, a polynucleotide of the present invention can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions. Non-limiting antisense and triple helix methods encompassed by the present invention are more thoroughly described elsewhere herein (see, e.g., the section labeled "Antisense and Ribozyme (Antagonists)").

[0358] Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell. Additional non-limiting examples of gene therapy methods encompassed by the present invention are more thoroughly described elsewhere

herein (see, e.g., the sections labeled "Gene Therapy Methods" and Examples 16, 17 and 18).

[0359] The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

[0360] The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

[0361] Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

[0362] There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or

primers prepared from the sequences of the present invention, specific to tissues, including but not limited to, those sequences referred to in Table 1A. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination. Additional non-limiting examples of such uses are further described herein.

[0363] Because connective tissue antigens are found expressed in connective tissue, the polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In a specific embodiment, the polynucleotides of the present invention are also useful as hybridization probes for differential identification of connective tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of connective tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, for example, normal connective tissues or diseased connective tissues, and/or those tissues/cells corresponding to the library source relating to a polynucleotide sequence of the invention as disclosed in column 7 of Table 1A, and/or cancerous and/or wounded tissues) or bodily fluids (e.g., semen, lymph, vaginal pool, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

[0364] Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of a disorder.

[0365] In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

[0366] Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

[0367] Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

[0368] Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (see, e.g., Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{131}I , ^{125}I , ^{123}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium ($^{115\text{m}}\text{In}$, $^{113\text{m}}\text{In}$, ^{112}In , ^{111}In), and technetium (^{99}Tc , $^{99\text{m}}\text{Tc}$), thallium (^{201}Tl), gallium (^{68}Ga , ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , ^{97}Ru ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0369] In addition to assaying levels of polypeptide of the present invention in a biological sample, proteins can also be detected *in vivo* by imaging. Antibody labels or markers for *in vivo* imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or

cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

[0370] A connective tissue antigen-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I , ^{112}In , $^{99\text{m}}\text{Tc}$, (^{131}I , ^{125}I , ^{123}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium ($^{115\text{m}}\text{In}$, $^{113\text{m}}\text{In}$, ^{112}In , ^{111}In), and technetium (^{99}Tc , $^{99\text{m}}\text{Tc}$), thallium (^{201}Tl), gallium (^{68}Ga , ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F , ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , ^{97}Ru), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a disorder of connective tissue(s). It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of $^{99\text{m}}\text{Tc}$. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0371] In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0372] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

[0373] In a preferred embodiment, the invention provides a method for the specific destruction of connective tissue cells (e.g., aberrant connective tissue cells, connective tissue neoplasm) by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) in association with toxins or cytotoxic prodrugs. In another preferred embodiment the invention provides a method for the specific destruction of tissues/cells corresponding to the library source relating to a polynucleotide sequence of the invention as disclosed in column 7 of Table 1A by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

[0374] By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ²¹³Bi, or other radioisotopes such as, for example, ¹⁰³Pd, ¹³³Xe, ¹³¹I, ¹¹¹In, ⁶⁸Ge, ⁵⁷Co, ⁶⁵Zn, ⁸⁵Sr, ³²P, ³⁵S, ⁹⁰Y, ¹⁵³Sm, ¹⁵³Gd, ¹⁶⁹Yb, ⁵¹Cr, ⁵⁴Mn, ⁷⁵Se, ¹¹³Sn, ⁹⁰Yttrium, ¹¹⁷Tin, ¹⁸⁶Rhenium, ¹⁶⁶Holmium, and ¹⁸⁸Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0375] In a specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ⁹⁰Y. In another specific embodiment, the invention provides a method for the specific destruction

of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{111}In . In a further specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{131}I .

[0376] Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

[0377] Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0378] Moreover, polypeptides of the present invention can be used to treat or prevent diseases or conditions of connective tissue such as, for example, rheumatoid arthritis, psoriatic arthritis, discoid lupus erythematosus, systemic lupus erythematosus, scleroderma, CREST syndrome, Sjogren's syndrome, polymyositis, dermatomyositis, mixed connective tissue disease, relapsing polychondritis, vasculitis, Henoch-Schonlein syndrome, erythema nodosum, polyarteritis nodosa, temporal (giant cell) arteritis, Takayasu's arteritis, Wegener's granulomatosis, Reiter's syndrome, Behcet's syndrome, ankylosing spondylitis, cellulitis, keloids, Ehler Danlos syndrome, Marfan syndrome, pseudoxantoma elasticum, osteogenesis imperfecta, chondrodysplasias, epidermolysis bullosa, Alport syndrome, cutis laxa, genetic disorders affecting skeleton, skin and

muscles; formation of excessive scar tissue; deposition of pathological amounts of connective tissue in body organs, including kidney, intestines and heart, and in liver by liver cirrhosis, in skin by scleroderma, in lung by lung fibrosis, in bone marrow by leukemia, in blood vessels by atherosclerosis, and in joints by rheumatic diseases. In preferred embodiments, polynucleotides expressed in a particular tissue type (see, e.g., Table 1A, column 7) are used to diagnose, detect, prevent, treat and/or prognose disorders associated with the tissue type. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

[0379] Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described *supra*, and elsewhere herein). For example, administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

[0380] At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the biological activities described herein.

Diagnostic Assays

[0381] The compounds of the present invention are useful for diagnosis, treatment,

prevention and/or prognosis of various connective tissue related disorders in mammals, preferably humans. Such disorders include, but are not limited to, rheumatoid arthritis, psoriatic arthritis, discoid lupus erythematosus, systemic lupus erythematosus, scleroderma, CREST syndrome, Sjogren's syndrome, polymyositis, dermatomyositis, mixed connective tissue disease, relapsing polychondritis, vasculitis, Henoch-Schonlein syndrome, erythema nodosum, polyarteritis nodosa, temporal (giant cell) arteritis, Takayasu's arteritis, Wegener's granulomatosis, Reiter's syndrome, Behcet's syndrome, ankylosing spondylitis, cellulitis, keloids, Ehler Danlos syndrome, Marfan syndrome, pseudoxantoma elasticum, osteogenesis imperfecta, chondrodysplasias, epidermolysis bullosa, Alport syndrome, cutis laxa, genetic disorders affecting skeleton, skin and muscles; formation of excessive scar tissue; deposition of pathological amounts of connective tissue in body organs, including kidney, intestines and heart, and in liver by liver cirrhosis, in skin by scleroderma, in lung by lung fibrosis, in bone marrow by leukemia, in blood vessels by atherosclerosis, and in joints by rheumatic diseases. In preferred embodiments, polynucleotides expressed in a particular tissue type (see, e.g., Table 1A, column 7) are used to diagnose, detect, prevent, treat and/or prognose disorders associated with the tissue type.

[0382] Connective tissue antigens are expressed in connective tissue. For a number of connective tissue-related disorders, substantially altered (increased or decreased) levels of connective tissue antigen gene expression can be detected in connective tissue or other cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" connective tissue antigen gene expression level, that is, the connective tissue antigen expression level in connective tissues or bodily fluids from an individual not having the connective tissue disorder. Thus, the invention provides a diagnostic method useful during diagnosis of a connective tissue disorder, which involves measuring the expression level of the gene encoding the connective tissue associated polypeptide in connective tissue or other cells or body fluid from an individual and comparing the measured gene expression level with a standard connective tissue antigens gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a connective tissue disorder.

[0383] In specific embodiments, the invention provides a diagnostic method useful

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during diagnosis of a disorder of a normal or diseased tissue/cell source corresponding to column 7 of Table 1A, which involves measuring the expression level of the coding sequence of a polynucleotide sequence associated with this tissue/cell source as disclosed in Table 1A in the tissue/cell source or other cells or body fluid from an individual and comparing the expression level of the coding sequence with a standard expression level of the coding sequence of a polynucleotide sequence, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a disorder of a normal or diseased tissue/cell source corresponding to column 7 of Table 1A.

[0384] In particular, it is believed that certain tissues in mammals with cancer of connective tissue(s) express significantly enhanced or reduced levels of normal or altered connective tissue antigen expression and mRNA encoding the connective tissue associated polypeptide when compared to a corresponding "standard" level. Further, it is believed that enhanced or depressed levels of the connective tissue associated polypeptide can be detected in certain body fluids (e.g., sera, plasma, urine, and spinal fluid) or cells or tissue from mammals with such a cancer when compared to sera from mammals of the same species not having the cancer.

[0385] For example, as disclosed herein, connective tissue associated polypeptides of the invention are expressed in connective tissue(s). Accordingly, polynucleotides of the invention (e.g., polynucleotide sequences complementary to all or a portion of a connective tissue antigen mRNA nucleotide sequence of SEQ ID NO:X, nucleotide sequence encoding SEQ ID NO:Y, nucleotide sequence encoding a polypeptide encoded by SEQ ID NO:X and/or a nucleotide sequence delineated by columns 8 and 9 of Table 2) and antibodies (and antibody fragments) directed against the polypeptides of the invention may be used to quantitate or qualitate concentrations of cells of connective tissue expressing connective tissue antigens, preferably on their cell surfaces. These polynucleotides and antibodies additionally have diagnostic applications in detecting abnormalities in the level of connective tissue antigens gene expression, or abnormalities in the structure and/or temporal, tissue, cellular, or subcellular location of connective tissue antigens. These diagnostic assays may be performed *in vivo* or *in vitro*, such as, for example, on blood samples, biopsy tissue or autopsy tissue. In specific embodiments, polynucleotides and antibodies of the invention are used to quantitate or qualitate tissues/cells corresponding to the library source disclosed in column 7 of Table 1A

expressing the corresponding connective tissue sequence disclosed in the same row of Table 1A, preferably on their cell surface.

[0386] Thus, the invention provides a diagnostic method useful during diagnosis of a connective tissue disorder, including cancers, which involves measuring the expression level of the gene encoding the connective tissue antigen polypeptide in connective tissue or other cells or body fluid from an individual and comparing the measured gene expression level with a standard connective tissue antigen gene expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a connective tissue disorder. In specific embodiments, polynucleotides and antibodies of the invention are used to quantitate or qualitate tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding connective tissue sequence disclosed in the same row of Table 1A, preferably on their cell surface.

[0387] Where a diagnosis of a disorder in connective tissue, including diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed connective tissue antigen gene expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[0388] By "assaying the expression level of the gene encoding the connective tissue associated polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the connective tissue antigen polypeptide or the level of the mRNA encoding the connective tissue antigen polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the connective tissue associated polypeptide level or mRNA level in a second biological sample). Preferably, the connective tissue antigen polypeptide expression level or mRNA level in the first biological sample is measured or estimated and compared to a standard connective tissue antigen polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having a disorder of connective tissue. As will be appreciated in the art, once a standard connective tissue antigen polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[0389] By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source containing connective tissue antigen polypeptides (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid) which contain cells expressing connective tissue antigen polypeptides, connective tissue, and other tissue sources found to express the full length or fragments thereof of a connective tissue antigen. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0390] Total cellular RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, Anal. Biochem. 162:156-159 (1987). Levels of mRNA encoding the connective tissue antigen polypeptides are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

[0391] The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of connective tissue antigen polypeptides, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of connective tissue antigens compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide, such as a connective tissue antigen polypeptide of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying connective tissue antigen polypeptide levels in a biological sample can occur using any art-known method.

[0392] Assaying connective tissue antigen polypeptide levels in a biological sample can occur using antibody-based techniques. For example, connective tissue antigen polypeptide expression in tissues can be studied with classical immunohistological

methods (Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting connective tissue antigen polypeptide gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (^{125}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{112}In), and technetium ($^{99\text{m}}\text{Tc}$), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0393] The tissue or cell type to be analyzed will generally include those which are known, or suspected, to express the connective tissue antigen gene (such as, for example, connective tissue cells or cancer of connective tissue). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the connective tissue antigen gene.

[0394] For example, antibodies, or fragments of antibodies, such as those described herein, may be used to quantitatively or qualitatively detect the presence of connective tissue antigen gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0395] In a preferred embodiment, antibodies, or fragments of antibodies directed to any one or all of the predicted epitope domains of the connective tissue antigen polypeptides (Shown in Table 1A, column 6) may be used to quantitatively or qualitatively detect the presence of connective tissue antigen gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0396] In an additional preferred embodiment, antibodies, or fragments of antibodies directed to a conformational epitope of a connective tissue antigen may be used to quantitatively or qualitatively detect the presence of connective tissue antigen gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0397] The antibodies (or fragments thereof), and/or connective tissue antigen polypeptides of the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of connective tissue antigen gene products or conserved variants or peptide fragments thereof. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or connective tissue antigen polypeptide of the present invention. The antibody (or fragment thereof) or connective tissue antigen polypeptide is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the connective tissue antigen gene product, or conserved variants or peptide fragments, or connective tissue antigen polypeptide binding, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

[0398] Immunoassays and non-immunoassays for connective tissue antigen gene products or conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of binding connective tissue antigen gene products or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

[0399] The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled anti-

connective tissue antigen antibody or detectable connective tissue antigen polypeptide. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or polypeptide. Optionally the antibody is subsequently labeled. The amount of bound label on solid support may then be detected by conventional means.

[0400] By "solid phase support or carrier" is intended any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

[0401] The binding activity of a given lot of anti-connective tissue antigen antibody or connective tissue antigen polypeptide may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

[0402] In addition to assaying connective tissue antigen polypeptide levels or polynucleotide levels in a biological sample obtained from an individual, connective tissue antigen polypeptide or polynucleotide can also be detected *in vivo* by imaging. For example, in one embodiment of the invention, connective tissue antigen polypeptide and/or anti-connective tissue antigen antibodies are used to image connective tissue diseased cells, such as neoplasms. In another embodiment, connective tissue antigen polynucleotides of the invention (e.g., polynucleotides complementary to all or a portion of connective tissue antigen mRNA) and/or anti-connective tissue antigen antibodies (e.g., antibodies directed to any one or a combination of the epitopes of connective tissue antigens, antibodies directed to a conformational epitope of connective tissue antigens, antibodies directed to the full length polypeptide expressed on the cell surface of a mammalian cell) are used to image diseased or neoplastic cells of connective tissue.

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[0403] Antibody labels or markers for *in vivo* imaging of connective tissue antigen polypeptides include those detectable by X-radiography, NMR, MRI, CAT-scans or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. Where *in vivo* imaging is used to detect enhanced levels of connective tissue antigen polypeptides for diagnosis in humans, it may be preferable to use human antibodies or "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using techniques described herein or otherwise known in the art. For example methods for producing chimeric antibodies are known in the art. See, for review, Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., *Nature* 312:643 (1984); Neuberger et al., *Nature* 314:268 (1985).

[0404] Additionally, any connective tissue antigen polypeptides whose presence can be detected, can be administered. For example, connective tissue antigen polypeptides labeled with a radio-opaque or other appropriate compound can be administered and visualized *in vivo*, as discussed, above for labeled antibodies. Further such connective tissue antigen polypeptides can be utilized for *in vitro* diagnostic procedures.

[0405] A connective tissue antigen polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I , ^{112}In , $^{99\text{m}}\text{Tc}$), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a connective tissue disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of $^{99\text{m}}\text{Tc}$. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain connective tissue antigen protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies

and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0406] With respect to antibodies, one of the ways in which the anti-connective tissue antigen antibody can be detectably labeled is by linking the same to an enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., *J. Clin. Pathol.* 31:507-520 (1978); Butler, J.E., *Meth. Enzymol.* 73:482-523 (1981); Maggio, E. (ed.), 1980, *Enzyme Immunoassay*, CRC Press, Boca Raton, FL.; Ishikawa, E. et al., (eds.), 1981, *Enzyme Immunoassay*, Kaku Shoin, Tokyo). The enzyme, which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

[0407] Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect connective tissue antigens through the use of a radioimmunoassay (RIA) (see, for example, Weintraub, B., *Principles of Radioimmunoassays*, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

[0408] It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its

presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescamine.

[0409] The antibody can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu , or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

[0410] The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, thionin acridinium ester, imidazole, acridinium salt and oxalate ester.

[0411] Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

Methods for Detecting Diseases of Connective Tissues(s), Including Cancer

[0412] In general, a connective tissue disease or cancer may be detected in a patient based on the presence of one or more connective tissue antigen proteins of the invention and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine, and/or tumor biopsies) obtained from the patient. In other words, such proteins and/or polynucleotides may be used as markers to indicate the presence or absence of a connective tissue disease or disorder, including cancer. Cancers that may be diagnosed, and/or prognosed using the compositions of the invention include but are not limited to, connective tissue cancer. In addition, such proteins and/or polynucleotides may be useful for the detection of other diseases and cancers, including cancers of tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding connective tissue sequence disclosed in the same row of Table 1A. The

binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding connective tissue antigen polypeptides, which is also indicative of the presence or absence of a connective tissue disease or disorder, including cancer. In general, connective tissue antigen polypeptides should be present at a level that is at least three fold higher in diseased tissue than in normal tissue.

[0413] There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *supra*. In general, the presence or absence of a connective tissue disease in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

[0414] In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the connective tissue antigen polypeptide of the invention from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include connective tissue antigen polypeptides and portions thereof, or antibodies, to which the binding agent binds, as described above.

[0415] The solid support may be any material known to those of skill in the art to which connective tissue antigen polypeptides of the invention may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The

support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for the suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 ug, and preferably about 100 ng to about 1 ug, is sufficient to immobilize an adequate amount of binding agent.

[0416] Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

Gene Therapy Methods

[0417] Also encompassed by the present invention are gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of a connective tissue antigen of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy

and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

[0418] Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldegrün, A., et al., *J. Natl. Cancer Inst.* 85: 207-216 (1993); Ferrantini, M. et al., *Cancer Research* 53: 1107-1112 (1993); Ferrantini, M. et al., *J. Immunology* 153: 4604-4615 (1994); Kaido, T., et al., *Int. J. Cancer* 60: 221-229 (1995); Ogura, H., et al., *Cancer Research* 50: 5102-5106 (1990); Santodonato, L., et al., *Human Gene Therapy* 7:1-10 (1996); Santodonato, L., et al., *Gene Therapy* 4:1246-1255 (1997); and Zhang, J.-F. et al., *Cancer Gene Therapy* 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells, which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

[0419] As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[0420] In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

[0421] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain

sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

[0422] Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoA1 promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

[0423] Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[0424] The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin

fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[0425] For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

[0426] The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[0427] The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

[0428] The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

[0429] In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al.,

J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

[0430] Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y., (see, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

[0431] Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

[0432] Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphosphatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[0433] For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or

by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

[0434] The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., *Methods of Immunology* (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca^{2+} -EDTA chelation (Papahadjopoulos et al., *Biochim. Biophys. Acta* (1975) 394:483; Wilson et al., *Cell* 17:77 (1979); ether injection (Deamer, D. and Bangham, A., *Biochim. Biophys. Acta* 443:629 (1976); Ostro et al., *Biochem. Biophys. Res. Commun.* 76:836 (1977); Fraley et al., *Proc. Natl. Acad. Sci. USA* 76:3348 (1979)); detergent dialysis (Enoch, H. and Strittmatter, P., *Proc. Natl. Acad. Sci. USA* 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., *J. Biol. Chem.* 255:10431 (1980); Szoka et al., *Proc. Natl. Acad. Sci. USA* 75:145 (1978); Schaefer-Ridder et al., *Science* 215:166 (1982)), which are herein incorporated by reference.

[0435] Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

[0436] U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466,

5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and International Publication No. WO 94/9469 provide methods for delivering DNA-cationic lipid complexes to mammals.

[0437] In certain embodiments, cells are engineered, *ex vivo* or *in vivo*, using a retroviral particle containing RNA, which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

[0438] The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and CaPO₄ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

[0439] The producer cell line generates infectious retroviral vector particles, which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express a polypeptide of the present invention.

[0440] In certain other embodiments, cells are engineered, *ex vivo* or *in vivo*, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent

safety profile (Schwartz, et al., Am. Rev. Respir. Dis.109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143-155 (1991)). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green et al., Proc. Natl. Acad. Sci. USA 76:6606 (1979)).

[0441] Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al., Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

[0442] Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

[0443] In certain other embodiments, the cells are engineered, ex vivo or *in vivo*, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example,

U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

[0444] For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles, which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either *ex vivo* or *in vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

[0445] Another method of gene therapy involves operably associating heterologous control regions and endogenous connective tissue antigen polynucleotide sequences (e.g., encoding a connective tissue antigen polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); and Zijlstra et al., *Nature* 342:435-438 (1989), which are herein incorporated by reference. This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

[0446] Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

[0447] The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

[0448] The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

[0449] The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

[0450] The polynucleotide encoding a polypeptide of the present invention may contain a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the connective tissue antigen polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

[0451] Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat

liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

[0452] A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

[0453] Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

[0454] Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site. In specific embodiments, suitable delivery vehicles for use with systemic administration comprise liposomes comprising polypeptides of the invention for targeting the vehicle to a particular site.

[0455] Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

[0456] Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological

activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

[0457] Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

Biological Activities

[0458] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat, prevent diagnose and/or prognose the associated disease.

[0459] The connective tissue antigen polynucleotides and polypeptides of the invention are predicted to have predominant expression in connective tissue(s).

[0460] Thus, the connective tissue antigens of the invention may be useful as therapeutic molecules. Each would be useful for diagnosis, detection, treatment and/or prevention of diseases or disorders of connective tissue, including but not limited to rheumatoid arthritis, psoriatic arthritis, discoid lupus erythematosus, systemic lupus erythematosus, scleroderma, CREST syndrome, Sjogren's syndrome, polymyositis, dermatomyositis, mixed connective tissue disease, relapsing polychondritis, vasculitis, Henoch-Schonlein syndrome, erythema nodosum, polyarteritis nodosa, temporal (giant cell) arteritis, Takayasu's arteritis, Wegener's granulomatosis, Reiter's syndrome, Behcet's syndrome, ankylosing spondylitis, cellulitis, keloids, Ehler Danlos syndrome, Marfan syndrome, pseudoxantoma elasticum, osteogenese imperfecta, chondrodysplasias, epidermolysis bullosa, Alport syndrome, cutis laxa, genetic disorders affecting skeleton, skin and muscles; formation of excessive scar tissue; deposition of pathological amounts

of connective tissue in body organs, including kidney, intestines and heart, and in liver by liver cirrhosis, in skin by scleroderma, in lung by lung fibrosis, in bone marrow by leukemia, in blood vessels by atherosclerosis, and in joints by rheumatic diseases.

[0461] In a preferred embodiment, polynucleotides of the invention (e.g., a nucleic acid sequence of SEQ ID NO:X or the complement thereof; or the cDNA sequence contained in Clone ID NO:Z, or fragments or variants thereof) and/or polypeptides of the invention (e.g., an amino acid sequence contained in SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, or the complement thereof, an amino acid sequence encoded by the cDNA sequence contained in Clone ID NO:Z and fragments or variants thereof as described herein) are useful for the diagnosis, detection, treatment, and/or prevention of diseases or disorders of the tissues/cells corresponding to the library source disclosed in column 7 of Table 1A expressing the corresponding connective tissue sequence disclosed in the same row of Table 1A.

[0462] Particularly, the connective tissue antigens may be a useful therapeutic for cancers of connective tissue(s). Treatment, diagnosis, detection, and/or prevention of connective tissue disorders could be carried out using a connective tissue antigen or soluble form of a connective tissue antigen, a connective tissue antigen ligand, gene therapy, or ex vivo applications. Moreover, inhibitors of a connective tissue antigen, either blocking antibodies or mutant forms, could modulate the expression of the connective tissue antigen. These inhibitors may be useful to treat, diagnose, detect, and/or prevent diseases associated with the misregulation of a connective tissue antigen.

[0463] Further, the connective tissue antigens may be useful for detecting changes in the neosynthesis of collagens that is indicative or suggestive of the malignant state of cells derived from such tumors as breast carcinomas.

[0464] In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells (e.g., normal or diseased connective tissue cells) by administering polypeptides of the invention (e.g., connective tissue antigen polypeptides or anti-connective tissue antigen antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell (e.g., an aberrant connective tissue cell or connective tissue cancer cell). In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or

ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0465] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of aberrant connective tissue cells, including, but not limited to, connective tissue tumor cells) by administering polypeptides of the invention (e.g., connective tissue antigen polypeptides or fragments thereof, or anti-connective tissue antigen antibodies) in association with toxins or cytotoxic prodrugs.

[0466] By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, cytotoxins (cytotoxic agents), or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi , or other radioisotopes such as, for example, ^{103}Pd , ^{133}Xe , ^{131}I , ^{68}Ge , ^{57}Co , ^{65}Zn , ^{85}Sr , ^{32}P , ^{35}S , ^{90}Y , ^{153}Sm , ^{153}Gd , ^{169}Yb , ^{51}Cr , ^{54}Mn , ^{75}Se , ^{113}Sn , $^{90}\text{Yttrium}$, ^{117}Tin , $^{186}\text{Rhenium}$, $^{166}\text{Holmium}$, and $^{188}\text{Rhenium}$; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0467] Techniques known in the art may be applied to label antibodies of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety). A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and

puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0468] By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

[0469] It will be appreciated that conditions caused by a decrease in the standard or normal level of a connective tissue antigen activity in an individual, particularly disorders of connective tissue, can be treated by administration of a connective tissue antigen polypeptide (e.g., such as, for example, the complete connective tissue antigen polypeptide, the soluble form of the extracellular domain of a connective tissue antigen polypeptide, or cells expressing the complete protein) or agonist. Thus, the invention also provides a method of treatment of an individual in need of an increased level of connective tissue antigen activity comprising administering to such an individual a pharmaceutical composition comprising an amount of an isolated connective tissue antigen polypeptide of the invention, or agonist thereof (e.g., an agonistic anti-connective tissue antigen antibody), effective to increase the connective tissue antigen activity level in such an individual.

[0470] It will also be appreciated that conditions caused by a increase in the standard or normal level of connective tissue antigen activity in an individual, particularly disorders of connective tissue, can be treated by administration of connective tissue antigen polypeptides (e.g., such as, for example, the complete connective tissue antigen polypeptide, the soluble form of the extracellular domain of a connective tissue antigen

polypeptide, or cells expressing the complete protein) or antagonist (e.g., an antagonistic connective tissue antigen antibody). Thus, the invention also provides a method of treatment of an individual in need of an decreased level of connective tissue antigen activity comprising administering to such an individual a pharmaceutical composition comprising an amount of an isolated connective tissue antigen polypeptide of the invention, or antagonist thereof (e.g., an antagonistic anti-connective tissue antigen antibody), effective to decrease the connective tissue antigen activity level in such an individual.

[0471] In certain embodiments, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 7 (Tissue Distribution Library Code).

[0472] More generally, polynucleotides, translation products and antibodies corresponding to this gene may be useful for the diagnosis, prognosis, prevention, and/or treatment of diseases and/or disorders associated with the following systems.

Immune Activity

[0473] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

[0474] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to

treat diseases and disorders of the immune system and/or to inhibit or enhance an immune response generated by cells associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 7 (Tissue Distribution Library Code).

[0475] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing, and/or prognosing immunodeficiencies, including both congenital and acquired immunodeficiencies. Examples of B cell immunodeficiencies in which immunoglobulin levels B cell function and/or B cell numbers are decreased include: X-linked agammaglobulinemia (Bruton's disease), X-linked infantile agammaglobulinemia, X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, X-linked lymphoproliferative syndrome (XLP), agammaglobulinemia including congenital and acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, unspecified hypogammaglobulinemia, recessive agammaglobulinemia (Swiss type), Selective IgM deficiency, selective IgA deficiency, selective IgG subclass deficiencies, IgG subclass deficiency (with or without IgA deficiency), Ig deficiency with increased IgM, IgG and IgA deficiency with increased IgM, antibody deficiency with normal or elevated Igs, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), common variable immunodeficiency (CVID), common variable immunodeficiency (CVI) (acquired), and transient hypogammaglobulinemia of infancy.

[0476] In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are treated, prevented, diagnosed, and/or prognosing using the polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof.

[0477] Examples of congenital immunodeficiencies in which T cell and/or B cell function and/or number is decreased include, but are not limited to: DiGeorge anomaly, severe combined immunodeficiencies (SCID) (including, but not limited to, X-linked SCID, autosomal recessive SCID, adenosine deaminase deficiency, purine nucleoside phosphorylase (PNP) deficiency, Class II MHC deficiency (Bare lymphocyte syndrome), Wiskott-Aldrich syndrome, and ataxia telangiectasia), thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia,

immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity.

[0478] In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, or antagonists or agonists thereof.

[0479] Other immunodeficiencies that may be treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, include, but are not limited to, chronic granulomatous disease, Chédiak-Higashi syndrome, myeloperoxidase deficiency, leukocyte glucose-6-phosphate dehydrogenase deficiency, X-linked lymphoproliferative syndrome (XLP), leukocyte adhesion deficiency, complement component deficiencies (including C1, C2, C3, C4, C5, C6, C7, C8 and/or C9 deficiencies), reticular dysgenesis, thymic aplasia, immunodeficiency with thymoma, severe congenital leukopenia, dysplasia with immunodeficiency, neonatal neutropenia, short limbed dwarfism, and Nezelof syndrome-combined immunodeficiency with Igs.

[0480] In a preferred embodiment, the immunodeficiencies and/or conditions associated with the immunodeficiencies recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0481] In a preferred embodiment polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among immunodeficient individuals. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

[0482] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides and polypeptides of the invention that

can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

[0483] Autoimmune diseases or disorders that may be treated, prevented, diagnosed and/or prognosed by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, one or more of the following: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, hemolytic anemia, thrombocytopenia, autoimmune thrombocytopenia purpura, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, purpura (e.g., Henoch-Schoenlein purpura), autoimmune cytopenia, Goodpasture's syndrome, Pemphigus vulgaris, myasthenia gravis, Grave's disease (hyperthyroidism), and insulin-resistant diabetes mellitus.

[0484] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome, autoimmune pulmonary inflammation, autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

[0485] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome

(often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

[0486] Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

[0487] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention. In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0488] In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0489] In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0490] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0491] In preferred embodiments, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a immunosuppressive agent(s).

[0492] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia. Alternatively, Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

[0493] Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, diagnosed and/or prognosed using polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

[0494] Additionally, polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, may be used to treat, prevent, diagnose and/or prognose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to,

asthma, rhinitis, and eczema. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

[0495] Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

[0496] Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, polynucleotides, polypeptides, and antibodies of the invention, as well as agonists or antagonists thereof, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adenitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chorditis, cochlitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis,

eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myositis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

[0497] In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

[0498] In other embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

[0499] Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively,

polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

[0500] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance tumor-specific immune responses.

[0501] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

[0502] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

[0503] In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom

selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Meissneria meningitidis*, *Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi*.

[0504] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria) or Leishmania.

[0505] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

[0506] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

[0507] In one embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

[0508] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell responsiveness to pathogens.

- [0509] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an activator of T cells.
- [0510] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.
- [0511] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to induce higher affinity antibodies.
- [0512] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to increase serum immunoglobulin concentrations.
- [0513] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to accelerate recovery of immunocompromised individuals.
- [0514] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.
- [0515] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.
- [0516] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or

antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

[0517] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

[0518] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonism of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

[0519] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

[0520] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

[0521] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodeficiency.

[0522] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in the pretreatment of bone marrow samples prior to transplant.

[0523] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence/immunodeficiency such as observed among SCID patients.

[0524] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

[0525] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

[0526] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in one or more of the applications described herein, as they may apply to veterinary medicine.

[0527] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

[0528] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

- [0529] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.
- [0530] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.
- [0531] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.
- [0532] The polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.
- [0533] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit complement mediated cell lysis.
- [0534] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.
- [0535] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.
- [0536] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed to treat adult respiratory distress syndrome (ARDS).

[0537] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.

[0538] In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with polynucleotides or polypeptides, and/or agonists of the present invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

[0539] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

[0540] In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, acute myelogenous

leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

[0541] In another specific embodiment, polypeptides; antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

[0542] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

[0543] In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

[0544] Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see, e.g., Example 9). Agonists of the invention include, for example, binding or stimulatory antibodies, and soluble forms of the polypeptides (e.g., Fc fusion proteins; see, e.g., Example 9). Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

[0545] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741). Administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention to such animals is useful for the generation of monoclonal antibodies against the polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention.

Blood-Related Disorders

[0546] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hemostatic (the stopping of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists or antagonists of the present invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

[0547] In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, diagnose, prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used for the prevention of occlusion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

[0548] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood

forming organs associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 7 (Tissue Distribution Library Code).

[0549] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets.. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for example eosinophilia.

[0550] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, treat, or diagnose blood dyscrasia.

[0551] Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary sideroblastic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune hemolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal

hemoglobinuria). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyl dopa, dapson, and/or sulfadiazine. Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

[0552] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to major and minor forms of alpha-thalassemia and beta-thalassemia.

[0553] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak syndromes, thromboxane A₂ dysfunction, thromboasthenia, and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophelias such as hemophilia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary Hemorrhagic Telangiectasia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

[0554] The effect of the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention on the clotting time of blood may be monitored using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or the Lee-White Clotting time.

[0555] Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in a specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

[0556] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders characterized by or associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body generates increased numbers of white blood cells during infection. Thus, leukocytosis may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer. Leukocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis.

[0557] Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in specific

embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia. Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency), neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment, anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

[0558] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies, and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndrome, severe combined immunodeficiency, ataxia telangiectasia).

[0559] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

[0560] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers

and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

[0561] In yet another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphoblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukemia), chronic myelocytic (myeloid, myelogenous, or granulocytic) leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

[0562] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

[0563] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myelod metaplasia, thrombocythemia, (including both primary and secondary thrombocythemia) and chronic myelocytic leukemia.

[0564] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as a treatment prior to surgery, to increase blood cell production.

[0565] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosinophils and macrophages.

[0566] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the

number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

[0567] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase cytokine production.

[0568] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

Hyperproliferative Disorders

[0569] Connective tissue associated polynucleotides or polypeptides, or agonists or antagonists thereof, can be used to treat, prevent, diagnose and/or prognose hyperproliferative diseases, disorders, and/or conditions, including neoplasms.

[0570] In a specific embodiment, connective tissue associated polynucleotides or polypeptides, or agonists or antagonists thereof, can be used to treat, prevent, and/or diagnose hyperproliferative diseases, disorders, and/or conditions of connective tissue(s).

[0571] In a preferred embodiment, connective tissue associated polynucleotides or polypeptides, or agonists or antagonists thereof, can be used to treat, prevent, and/or diagnose connective tissue neoplasms.

[0572] Connective tissue associated polynucleotides or polypeptides, or agonists or antagonists of the invention, may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, connective tissue associated polynucleotides or polypeptides, or agonists or antagonists thereof, may proliferate other cells, which can inhibit the hyperproliferative disorder.

[0573] For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative diseases, disorders, and/or conditions can be treated, prevented, and/or diagnosed. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating,

preventing, and/or diagnosing hyperproliferative diseases, disorders, and/or conditions, such as a chemotherapeutic agent.

[0574] Examples of hyperproliferative diseases, disorders, and/or conditions that can be treated, prevented, and/or diagnosed by connective tissue associated polynucleotides or polypeptides, or agonists or antagonists thereof, include, but are not limited to neoplasms located in the: prostate, colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

[0575] Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-

Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer,

Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0576] In another preferred embodiment, polynucleotides or polypeptides, or agonists or antagonists of the present invention are used to diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

[0577] Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous hyperplasia, and verrucous hyperplasia.

[0578] Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial

metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

[0579] Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, anhidrotic ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atriopigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, faciogenital dysplasia, familial fibrous dysplasia of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, oculovertbral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

[0580] Additional pre-neoplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy,

intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

[0581] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, 7 (Tissue Distribution Library Code).

[0582] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including, but not limited to those described herein. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat acute myelogenous leukemia.

[0583] Additionally, polynucleotides, polypeptides, and/or agonists or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[0584] In preferred embodiments, polynucleotides, polypeptides, and/or agonists or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

[0585] Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[0586] Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's

thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

[0587] Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

[0588] Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstrom's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0589] One preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

[0590] Thus, the present invention provides a method for treating cell proliferative diseases, disorders, and/or conditions by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said cell proliferation, disease, disorder, and/or condition.

[0591] In a preferred embodiment, the present invention provides a method for treating cell proliferative diseases, disorders and/or conditions of connective tissue(s) by inserting into a cell, a polynucleotide of the present invention, wherein said polynucleotide represses said cell proliferation, disease and/or disorder.

2025-11-19 14:30:00

[0592] Another embodiment of the present invention provides a method of treating cell-proliferative diseases, disorders, and/or conditions in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (see, e.g., G J. Nabel, et. al., PNAS 96: 324-326 (1999), which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e., magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e., to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

[0593] Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

[0594] For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al.,

Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

[0595] The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

[0596] By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

[0597] Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

[0598] The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described diseases,

disorders, and/or conditions. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0599] A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g., as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[0600] In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation diseases, disorders, and/or conditions as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

[0601] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[0602] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of diseases, disorders, and/or conditions related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments thereof. Preferred binding affinities include those with a dissociation constant or K_d less than $5 \times 10^{-6}M$, $10^{-6}M$, $5 \times 10^{-7}M$, $10^{-7}M$, $5 \times 10^{-8}M$, $10^{-8}M$, $5 \times 10^{-9}M$, $10^{-9}M$, $5 \times 10^{-10}M$, $10^{-10}M$, $5 \times 10^{-11}M$, $10^{-11}M$, $5 \times 10^{-12}M$, $10^{-12}M$, $5 \times 10^{-13}M$, $10^{-13}M$, $5 \times 10^{-14}M$, $10^{-14}M$, $5 \times 10^{-15}M$, and $10^{-15}M$.

[0603] Moreover, connective tissue antigen polypeptides of the present invention or fragments thereof, are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (see, e.g., Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (see, e.g., Witte L, et al., Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

[0604] Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (see, e.g., Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, antiinflammatory proteins (See for example, Mutat. Res. 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem. Biol. Interact. Apr 24;111-112:23-34 (1998), J. Mo. Med. 76(6):402-12 (1998), Int. J. Tissue React. 20(1):3-15 (1998), which are all hereby incorporated by reference).

[0605] Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See,

e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

[0606] In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or anti-connective tissue antigen polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Connective tissue antigen polypeptides or anti-connective tissue antigen polypeptide antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

[0607] Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

Urinary System Disorders

[0608] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the urinary system, including but not limited to disorders of the renal system, bladder, ureters, and urethra. Renal disorders include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

[0609] Kidney failure diseases include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, and end-stage renal disease. Inflammatory diseases of the kidney include acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic

glomerulonephritis, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal glomerulonephritis.

[0610] Blood vessel disorders of the kidneys include, but are not limited to, kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal ischemia-reperfusion, renal artery embolism, and renal artery stenosis. Kidney disorders resulting from urinary tract problems include, but are not limited to, pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.

[0611] Metabolic and congenital disorders of the kidneys include, but are not limited to, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, vitamin D-resistant rickets, Hartnup disease, Bartter's syndrome, Liddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy. Kidney disorders resulting from an autoimmune response include, but are not limited to, systemic lupus erythematosus (SLE), Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis.

[0612] Sclerotic or necrotic disorders of the kidney include, but are not limited to, glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis. Kidneys may also develop carcinomas, including, but not limited to, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, squamous cell cancer, and Wilm's tumor.

[0613] Kidney disorders may also result in electrolyte imbalances, including, but not limited to, nephrocalcinosis, pyuria, edema, hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia.

[0614] Bladder disorders include, but are not limited to, benign prostatic hyperplasia (BPH), interstitial cystitis (IC), prostatitis, proteinuria, urinary tract infections, urinary incontinence, urinary retention. Disorders of the ureters and urethra include, but are not

limited to, acute or chronic unilateral obstructive uropathy. The bladder, ureters, and urethra may also develop carcinomas, including, but not limited to, superficial bladder cancer, invasive bladder cancer, carcinoma of the ureter, and urethra cancers.

[0615] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Cardiovascular Disorders

[0616] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

[0617] Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, total anomalous pulmonary venous connection, hypoplastic left heart syndrome, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, atrioventricular canal defect, trilogly of Fallot, ventricular heart septal defects.

[0618] Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, sudden cardiac death, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right

ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, diastolic dysfunction, enlarged heart, heart block, J-curve phenomenon, rheumatic heart disease, Marfan syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

[0619] Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

[0620] Heart valve disease include aortic valve insufficiency, aortic valve stenosis, heart murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, tricuspid valve stenosis, and bicuspid aortic valve.

[0621] Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, Barth syndrome, myocardial reperfusion injury, and myocarditis.

[0622] Myocardial ischemias include coronary disease, such as angina pectoris, Prinzmetal's angina, unstable angina, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

[0623] Cardiovascular diseases also include vascular diseases such as aneurysms, angiodyplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension (shock), ischemia, peripheral vascular diseases, phlebitis, superficial phlebitis, pulmonary veno-occlusive disease, chronic obstructive pulmonary disease, Buerger's disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, deep vein thrombosis, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

[0624] Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

[0625] Arterial occlusive diseases include arteriosclerosis, arteriolosclerosis, atherosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

[0626] Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

[0627] Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, deep vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

[0628] Ischemia includes cerebral ischemia, ischemic colitis, silent ischemia, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

[0629] Cardiovascular diseases can also occur due to electrolyte imbalances that include, but are not limited to hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia. Neoplasm and/or cancers of the cardiovascular system include, but are not limited to, myxomas, fibromas, and rhabdomyomas.

[0630] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Respiratory Disorders

[0631] Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

[0632] Diseases and disorders of the respiratory system include, but are not limited to, nasal vestibulitis, nonallergic rhinitis (e.g., acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose and juvenile papillomas, vocal cord polyps, nodules (singer's nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (e.g., viral and bacterial), tonsillitis, tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (e.g., cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (e.g., squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and

adenocarcinoma), allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (e.g., extrinsic allergic alveolitis, allergic interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (e.g., bacterial pneumonia (e.g., *Streptococcus pneumoniae* (pneumococcal pneumonia), *Staphylococcus aureus* (staphylococcal pneumonia), Gram-negative bacterial pneumonia (caused by, e.g., *Klebsiella* and *Pseudomonas spp.*), *Mycoplasma pneumoniae* pneumonia, *Hemophilus influenzae* pneumonia, *Legionella pneumophila* (Legionnaires' disease), and *Chlamydia psittaci* (Psittacosis)), and viral pneumonia (e.g., influenza, chickenpox (varicella).

[0633] Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, german measles, and subacute sclerosing panencephalitis), fungal pneumonia (e.g., Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal infections in people with severely suppressed immune systems (e.g., cryptococcosis, caused by *Cryptococcus neoformans*; aspergillosis, caused by *Aspergillus spp.*; candidiasis, caused by *Candida*; and mucormycosis)), *Pneumocystis carinii* (pneumocystis pneumonia), atypical pneumonias (e.g., *Mycoplasma* and *Chlamydia spp.*), opportunistic infection pneumonia, nosocomial pneumonia, chemical pneumonitis, and aspiration pneumonia, pleural disorders (e.g., pleurisy, pleural effusion, and pneumothorax (e.g., simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthma, byssinosis, and benign pneumoconioses), Infiltrative Lung Disease (e.g., pulmonary fibrosis (e.g., fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis X (e.g., Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (e.g., viral,

bacterial), bronchiectasis, atelectasis, lung abscess (caused by, e.g., *Staphylococcus aureus* or *Legionella pneumophila*), and cystic fibrosis.

Anti-Angiogenesis Activity

[0634] The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell* 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, 333:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Ophthalmol.* 94:715-743 (1982); and Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science* 235:442-447 (1987).

[0635] The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, *Medicine*, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administration to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide,

antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

[0636] Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

[0637] Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's

disease; and atherosclerosis.

[0638] For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

[0639] Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists of the invention are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

[0640] Moreover, ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al.*, *Am. J. Ophthalm.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalm.* 22:291-312 (1978).

[0641] Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue, which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the

patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

[0642] Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer, which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

[0643] Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation, the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form, injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection

itself.

[0644] Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

[0645] Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

[0646] Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreal injection and/or via intraocular implants.

[0647] Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or antagonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

[0648] Moreover, disorders and/or states, which can be treated, prevented, diagnosed and/or prognosed with the polynucleotides, polypeptides, agonists and/or antagonists of the invention include, but are not limited to, solid tumors, blood born tumors such as

leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (*Rochelominalia quintosa*), ulcers (*Helicobacter pylori*), Bartonellosis and bacillary angiomatosis.

[0649] In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or antagonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

[0650] Polynucleotides, polypeptides, agonists and/or antagonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

[0651] Polynucleotides, polypeptides, agonists and/or antagonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a composition (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes, which have been coated with anti-angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be

utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

[0652] Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or antagonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

[0653] Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or antagonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

[0654] The polynucleotides, polypeptides, agonists and/or antagonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[0655] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[0656] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[0657] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[0658] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26 (1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326 (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480 (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557 (1990)); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446 (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes

et al., J. Biol. Chem. 262(4):1659-1664 (1987)); Bisantrone (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

Musculoskeletal System Disorders

- [0659] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the musculoskeletal system, including but not limited to, disorders of the bone, joints, ligaments, tendons, bursa, muscle, and/or neoplasms and cancers associated with musculoskeletal tissue.
- [0660] Diseases or disorders of the bone include, but are not limited to, Albers-Schönberg disease, bowlegs, heel spurs, Köhler's bone disease, knock-knees, Legg-Calvé-Perthes disease, Marfan's syndrome, mucopolysaccharidoses, Osgood-Schlatter disease, osteochondroses, osteochondrodysplasia, osteomyelitis, osteopetroses, osteoporosis (postmenopausal, senile, and juvenile), Paget's disease, Scheuermann's disease, scoliosis, Sever's disease, and patellofemoral stress syndrome.
- [0661] Joint diseases or disorders include, but are not limited to, ankylosing spondylitis, Behçet's syndrome, CREST syndrome, Ehlers-Danlos syndrome, infectious arthritis, discoid lupus erythematosus, systemic lupus erythematosus, Lyme disease, osteoarthritis, psoriatic arthritis, relapsing polychondrites, Reiter's syndrome, rheumatoid arthritis (adult and juvenile), scleroderma, and Still's disease.
- [0662] Diseases or disorders affecting ligaments, tendons, or bursa include, but are not limited to, ankle sprain, bursitis, posterior Achilles tendon bursitis (Haglund's deformity), anterior Achilles tendon bursitis (Albert's disease), tendinitis, tenosynovitis, popliteus tendinitis, Achilles tendinitis, medial or lateral epicondylitis, rotator cuff tendinitis, spasmodic torticollis, and fibromyalgia syndrome.
- [0663] Muscle diseases or disorders include, but are not limited to, Becker's muscular dystrophy, Duchenne's muscular dystrophy, Landouzy-Dejerine muscular dystrophy, Leyden-Möbius muscular dystrophy, Erb's muscular dystrophy, Charcot's joints, dermatomyositis, gout, pseudogout, glycogen storage diseases, Pompe's disease, mitochondrial myopathy, periodic paralysis, polymyalgia rheumatica, polymyositis,

Steinert's disease, Thomsen's disease, anterolateral and posteromedial shin splints, posterior femoral muscle strain, and fibromyositis.

[0664] Musculoskeletal tissue may also develop cancers and/or neoplasms that include, but are not limited to, osteochondroma, benign chondroma, chondroblastoma, chondromyxoid fibroma, osteoid osteoma, giant cell tumor, multiple myeloma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's tumor, and malignant lymphoma of bone.

Neural Activity and Neurological Diseases

[0665] The polynucleotides, polypeptides and agonists or antagonists of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be treated with the compositions of the invention (e.g., polypeptides, polynucleotides, and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral

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sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

[0666] In one embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

[0667] In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

[0668] In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, the polypeptides,

polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

[0669] The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, e.g., choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, 10:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al.*, *Exp. Neurol.*, 70:65-82 (1980), or Brown *et al.*, *Ann. Rev. Neurosci.*, 4:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

[0670] In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

[0671] Further, polypeptides or polynucleotides of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including polynucleotides, polypeptides, and agonists or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

[0672] Additionally, polypeptides, polynucleotides and/or agonists or antagonists of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

[0673] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or

detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

[0674] Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

[0675] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

[0676] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as

Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

[0677] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

[0678] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis which includes lymphocytic choriomeningitis, Bacterial meningitis which includes Haemophilus Meningitis, Listeria Meningitis, Meningococcal Meningitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-

Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

[0679] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral scleritis which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon-Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucopolysaccharidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydranencephaly, Arnold-Chiari Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

[0680] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-

Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyoclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-

Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

[0681] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

Endocrine Disorders

[0682] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine system.

[0683] Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to

respond to hormones. The etiology of these hormone imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

[0684] Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

[0685] Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

[0686] In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells, cryptorchidism,

Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

[0687] Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

[0688] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose, prognose, prevent, and/or treat endocrine diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 1A, column 7 (Tissue Distribution Library Code).

Gastrointestinal Disorders

[0689] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowel lymphoma)), and ulcers, such as peptic ulcers.

[0690] Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperitoneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess).

[0691] Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum,

Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata*, *Echinococcus granulosus*, *Diphyllobothrium spp.*, and *T. solium*).

[0692] Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolenticular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma,

cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Kaposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome).

[0693] Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

[0694] Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

[0695] Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoid neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption

syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowel syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis.

[0696] Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

Reproductive System Disorders

[0697] The polynucleotides or polypeptides, or agonists or antagonists of the invention may be used for the diagnosis, treatment, or prevention of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

[0698] Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including, but not limited to, testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

[0699] Reproductive system disorders also include, but are not limited to, disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

[0700] Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including, but not limited to, inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid papulosis, giant

condyloma of Buscke-Lowenstein, and verrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and impotence.

[0701] Moreover, diseases and/or disorders of the vas deferens include, but are not limited to, vasculitis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the seminal vesicles, including but not limited to, hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

[0702] Other disorders and/or diseases of the male reproductive system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

[0703] Further, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the vagina and vulva, including, but not limited to, bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

[0704] Disorders and/or diseases of the uterus that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding

(e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, leiomyosarcomas, and sarcomas. Additionally, the polypeptides, polynucleotides, or agonists or antagonists of the invention may be useful as a marker or detector of, as well as in the diagnosis, treatment, and/or prevention of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelphys, and T-shaped uterus.

[0705] Ovarian diseases and/or disorders that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirsutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometrioid carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

[0706] Cervical diseases and/or disorders that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

[0707] Additionally, diseases and/or disorders of the reproductive system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists

of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism, Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders, and obstruction of the intestine.

[0708] Complications associated with labor and parturition that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

[0709] Further, diseases and/or disorders of the postdelivery period, that may be diagnosed, treated, and/or prevented with the compositions of the invention, include, but are not limited to, endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

[0710] Other disorders and/or diseases of the female reproductive system that may be diagnosed, treated, and/or prevented by the polynucleotides, polypeptides, and agonists or antagonists of the present invention include, but are not limited to, Turner's syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

Developmental and Inherited Disorders

[0711] Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be used to treat, prevent, diagnose, and/or prognose diseases associated with mixed fetal tissues, including, but not limited to, developmental and inherited disorders or defects of the nervous system, musculoskeletal system, excretory system,

cardiovascular system, hematopoietic system, gastrointestinal system, reproductive system, and respiratory system. Compositions of the present invention may also be used to treat, prevent, diagnose, and/or prognose developmental and inherited disorders or defects associated with, but not limited to, skin, hair, visual, and auditory tissues, metabolism. Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases associated with, but not limited to, chromosomal or genetic abnormalities and hyperproliferation or neoplasia.

[0712] Disorders or defects of the nervous system associated with developmental or inherited abnormalities that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, adrenoleukodystrophy, agenesis of corpus callosum, Alexander disease, anencephaly, Angelman syndrome, Arnold-Chiari deformity, Batten disease, Canavan disease, cephalic disorders, Charcot-Marie-Tooth disease, encephalocele, Friedreich's ataxia, Gaucher's disease, Gorlin syndrome, Hallervorden-Spatz disease, hereditary spastic paraplegia, Huntington disease, hydranencephaly, hydrocephalus, Joubert syndrome, Lesch-Nyhan syndrome, leukodystrophy, Menkes disease, microcephaly, Niemann-Pick Type C1, neurofibromatosis, porencephaly, progeria, proteus syndrome, Refsum disease, spina bifida, Sturge-Weber syndrome, Tay-Sachs disease, tuberous sclerosis, and von Hippel-Lindau disease.

[0713] Developmental and inherited disorders resulting in disorders or defects of the musculoskeletal system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, achondroplasia, atlanto-occipital fusion, arthrogryposis multiplex congenita, autosomal recessive muscular dystrophy, Becker's muscular dystrophy, cerebral palsy, choanal atresia, cleft lip, cleft palate, clubfoot, congenital amputation, congenital dislocation of the hip, congenital torticollis, congenital scoliosis, dopa-responsive dystonia, Duchenne muscular dystrophy, early-onset generalized dystonia, femoral torsion, Gorlin syndrome, hypophosphatasia, Klippel-Feil syndrome, knee dislocation, myoclonic dystonia, myotonic dystrophy, nail-patella syndrome, osteogenesis imperfecta, paroxysmal dystonia, progeria, prune-belly syndrome, rapid-onset dystonia parkinsonism, scoliosis, syndactyly, Treacher Collins' syndrome, velocardiofacial syndrome, and X-linked dystonia-parkinsonism.

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[0714] Developmental or hereditary disorders or defects of the excretory system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, Alport's syndrome, Bartter's syndrome, bladder diverticula, bladder exstrophy, cystinuria, epispadias, Fanconi's syndrome, Hartnup disease, horseshoe kidney, hypospadias, kidney agenesis, kidney ectopia, kidney malrotation, Liddle's syndrome, medullary cystic disease, medullary sponge, multicystic kidney, kidney polycystic kidney disease, nail-patella syndrome, Potter's syndrome, urinary tract flow obstruction, vitamin D-resistant rickets, and Wilm's tumor.

[0715] Cardiovascular disorders or defects of developmental or hereditary origin that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, aortic valve stenosis, atrial septal defects, artioventricular (A-V) canal defect, bicuspid aortic valve, coarctation of the aorta, dextrocardia, Ebstein's anomaly, Eisenmenger's complex, hypoplastic left heart syndrome, Marfan syndrome, patent ductus arteriosus, progeria, pulmonary atresia, pulmonary valve stenosis, subaortic stenosis, tetralogy of fallot, total anomalous pulmonary venous (P-V) connection, transposition of the great arteries, tricuspid atresia, truncus arteriosus, ventricular septal defects. Developmental or inherited disorders resulting in disorders involving the hematopoietic system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but not limited to, Bernard-Soulier syndrome, Chédiak-Higashi syndrome, hemophilia, Hermansky-Pudlak syndrome, sickle cell anemia, storage pool disease, thromboxane A2 dysfunction, thrombasthenia, and von Willebrand's disease.

[0716] The compositions of the invention may also be used to diagnose, treat, and/or prevent developmental and inherited disorders resulting in disorders or defects of the gastrointestinal system, including, but not limited to, anal atresia, biliary atresia, esophageal atresia, diaphragmatic hernia, Hirschsprung's disease, Meckel's diverticulum, oligohydramnios, omphalocele, polyhydramnios, porphyria, situs inversus viscera. Developmental or inherited disorders resulting in metabolic disorders that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, alpha-1 antitrypsin deficiency, cystic fibrosis, hemochromatosis, lysosomal storage disease, phenylketonuria, Wilson's disease, and Zellweger syndrome.

[0718] Developmental or inherited disorders may also result from chromosomal or genetic aberration that may be diagnosed, treated, and/or prevented with the compositions of the invention including, but not limited to, 4p- syndrome, cri du chat syndrome, Digeorge syndrome, Down's syndrome, Edward's syndrome, fragile X syndrome, Klinefelter's syndrome, Patau's syndrome, Prader-Willi syndrome, progeria, Turner's syndrome, triple X syndrome, and XYY syndrome. Other developmental disorders that can be diagnosed, treated, and/or prevented with the compositions of the invention, include, but are not limited to, fetal alcohol syndrome, and can be caused by environmental factors surrounding the developing fetus.

[0719] The compositions of the invention may further be able to be used to diagnose, treat, and/or prevent errors in development or a genetic disposition that may result in hyperproliferative disorders or neoplasms, including, but not limited to, acute childhood lymphoblastic leukemia, askin tumor, Beckwith-Wiedemann syndrome, childhood acute myeloid leukemia, childhood brain stem glioma, childhood cerebellar astrocytoma, childhood extracranial germ cell tumors childhood (primary), gonadoblastoma, hepatocellular cancer, childhood Hodgkin's disease, childhood Hodgkin's lymphoma, childhood hypothalamic and visual pathway glioma, childhood (primary) liver cancer, childhood lymphoblastic leukemia, childhood medulloblastoma, childhood non-Hodgkin's lymphoma, childhood pineal and supratentorial primitive neuroectodermal tumors, childhood primary liver cancer, childhood rhabdomyosarcoma, childhood soft tissue sarcoma, Gorlin syndrome, familial multiple endocrine neoplasia type I, neuroblastoma, ovarian germ cell cancer, pheochromocytoma, retinoblastoma, and Wilm's tumor.

[0720] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Diseases at the Cellular Level

[0721] Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, diagnosed and/or prognosed using polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[0722] In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those [listed above] involving connective tissue.

[0723] Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic,

promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[0724] Diseases associated with increased apoptosis that could be treated, prevented, diagnosed, and/or prognosed using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include, but are not limited to, AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Wound Healing and Epithelial Cell Proliferation

[0725] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss.

[0726] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepidermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omentopial graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

[0727] It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small

intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

[0728] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

[0729] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases, which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and

could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associate with the under expression.

[0730] Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate proliferation and differentiation and promote the repair of alveoli and brochiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary dislasia, in premature infants.

[0731] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

[0732] In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

Infectious Disease

[0733] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

[0734] Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papilloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat:

meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

[0735] Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, include, but not limited to, the following Gram-Negative and Gram-positive bacteria and bacterial families and fungi: Actinomycetales (e.g., *Corynebacterium*, *Mycobacterium*, *Nocardia*), *Cryptococcus neoformans*, Aspergillosis, Bacillaceae (e.g., Anthrax, *Clostridium*), Bacteroidaceae, Blastomycosis, *Bordetella*, *Borrelia* (e.g., *Borrelia burgdorferi*, Brucellosis, Candidiasis, *Campylobacter*, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), Enterobacteriaceae (*Klebsiella*, *Salmonella* (e.g., *Salmonella typhi*, and *Salmonella paratyphi*), *Serratia*, *Yersinia*), *Erysipelothrix*, *Helicobacter*, Legionellosis, Leptospirosis, *Listeria*, Mycoplasmatales, *Mycobacterium leprae*, *Vibrio cholerae*, Neisseriaceae (e.g., *Acinetobacter*, Gonorrhea, Meningococcal), *Meisseria meningitidis*, Pasteurellacea Infections (e.g., *Actinobacillus*, *Heamophilus* (e.g., *Heamophilus influenza* type B), *Pasteurella*), *Pseudomonas*, Rickettsiaceae, Chlamydiaceae, *Treponema* spp., *Leptospira* spp., *Shigella* spp., Staphylococcal, Meningiococcal, Pneumococcal and Streptococcal (e.g., *Streptococcus pneumoniae* and Group B *Streptococcus*). These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis (e.g., meningitis types A and B), Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. Polynucleotides or polypeptides, agonists or antagonists of

the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, Polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, Diphtheria, botulism, and/or meningitis type B.

[0736] Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., Plasmodium virax, Plasmodium falciparum, Plasmodium malariae and Plasmodium ovale). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases.

[0737] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

[0738] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

[0739] Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

[0740] Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

[0741] Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

Chemotaxis

[0742] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation,

infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

[0743] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

[0744] It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

[0745] A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

[0746] Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

[0747] Preferably, the screening for these molecules involves producing appropriate cells, which express the polypeptide. Preferred cells include cells from mammals, yeast,

Drosophila, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

[0748] The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

[0749] Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

[0750] Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

[0751] Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labeled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

[0752] Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-

transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

[0753] As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

[0754] Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. See generally, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, S. Trends Biotechnol. 16(2):76-82 (1998); Hansson L. O., et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. Biotechniques 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor

(FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

[0755] Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[0756] Additionally, this invention provides a method of screening compounds to identify those, which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, the polypeptide of the present invention, the compound to be screened and $^3\text{[H]}$ thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of $^3\text{[H]}$ thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography, which measures the incorporation of $^3\text{[H]}$ thymidine. Both agonist and antagonist compounds may be identified by this procedure.

[0757] In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

[0758] All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the

polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

[0759] Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Targeted Delivery

[0760] In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

[0761] As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0762] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

[0763] By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins,

or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

Drug Screening

[0764] Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules, which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

[0765] This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

[0766] Thus, the present invention provides methods of screening for drugs or any other agents, which affect activities mediated by the polypeptides of the present

invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

[0767] Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

[0768] This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

Antisense And Ribozyme (Antagonists)

[0769] In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to cDNA sequences contained in cDNA Clone ID NO:Z identified for example, in Table 1A. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991)).

Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

[0770] For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed *in vitro* by incubating cells with the oligoribonucleotide. A similar procedure for *in vivo* use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoR1 site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl₂, 10MM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoR1/Hind III site of the retroviral vector PMV7 (WO 91/15580):

[0771] For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into receptor polypeptide.

[0772] In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can

be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invention or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, *Nature* 29:304-310 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell* 22:787-797 (1980)), the herpes thymidine promoter (Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.* 78:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster, et al., *Nature* 296:39-42 (1982)), etc.

[0773] The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

[0774] Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, *Nature* 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of polynucleotide sequences described herein could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG

start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

[0775] The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

[0776] The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil,

5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

[0777] The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

[0778] In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

[0779] In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

[0780] Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

[0781] While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

[0782] Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target

mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

[0783] As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express *in vivo*. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

[0784] Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

[0785] The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirable in cases such as restenosis after balloon angioplasty.

[0786] The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

[0787] The antagonist/agonist may also be employed to treat the diseases described herein.

[0788] Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application,

associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

Binding Peptides and Other Molecules

[0789] The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind connective tissue antigen polypeptides, and the connective tissue antigen binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the connective tissue antigen polypeptides. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

[0790] This method comprises the steps of:

contacting connective tissue antigen polypeptides or connective tissue antigen-like polypeptides with a plurality of molecules; and

identifying a molecule that binds the connective tissue antigen polypeptides or connective tissue antigen-like polypeptides.

[0791] The step of contacting the connective tissue antigen polypeptides or connective tissue antigen-like polypeptides with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the connective tissue antigen polypeptides or connective tissue antigen-like polypeptides on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized connective tissue antigen polypeptides or connective tissue antigen-like polypeptides. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized connective tissue antigen polypeptides or connective tissue antigen-like polypeptides. The molecules having a selective affinity for the connective tissue antigen polypeptides or connective tissue antigen-like polypeptides can then be purified by affinity selection. The nature of the solid support, process for attachment of the connective tissue antigen polypeptides or connective tissue antigen-like polypeptides to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

tissue antigen polypeptides or connective tissue antigen-like polypeptides or the plurality of polypeptides is bound to a solid support.

[0794] The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind connective tissue antigen polypeptides. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and *in vitro* translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, Science 251:767-773; Houghten et al., 1991, Nature 354:84-86; Lam et al., 1991, Nature 354:82-84; Medynski, 1994, Bio/Technology 12:709-710; Gallop et al., 1994, J. Medicinal Chemistry 37(9):1233-1251; Ohlmeyer et al., 1993, Proc. Natl. Acad. Sci. USA 90:10922-10926; Erb et al., 1994, Proc. Natl. Acad. Sci. USA 91:11422-11426; Houghten et al., 1992, Biotechniques 13:412; Jayawickreme et al., 1994, Proc. Natl. Acad. Sci. USA 91:1614-1618; Salmon et al., 1993, Proc. Natl. Acad. Sci. USA 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381-5383.

[0795] Examples of phage display libraries are described in Scott and Smith, 1990, Science 249:386-390; Devlin et al., 1990, Science, 249:404-406; Christian, R. B., et al., 1992, J. Mol. Biol. 227:711-718; Lenstra, 1992, J. Immunol. Meth. 152:149-157; Kay et al., 1993, Gene 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

[0796] *In vitro* translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

[0797] By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

[0798] The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list

benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

[0799] Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

[0800] Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

[0801] Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott and Smith, 1990, Science 249:386-390; Fowlkes et al., 1992, BioTechniques 13:422-427; Oldenburg et al., 1992, Proc. Natl. Acad. Sci. USA 89:5393-5397; Yu et al., 1994, Cell 76:933-945; Staudt et al., 1988, Science 241:577-580; Bock et al., 1992, Nature 355:564-566; Tuerk et al., 1992, Proc. Natl. Acad. Sci. USA 89:6988-6992; Ellington et al., 1992, Nature 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, Science 263:671-673; and CT Publication No. WO 94/18318.

[0802] In a specific embodiment, screening to identify a molecule that binds connective tissue antigen polypeptides can be carried out by contacting the library members with a connective tissue antigen polypeptides or connective tissue antigen-like polypeptides immobilized on a solid phase and harvesting those library members that bind to the connective tissue antigen polypeptides or connective tissue antigen-like

polypeptides. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, Gene 73:305-318; Fowlkes et al., 1992, BioTechniques 13:422-427; International Publication No. WO 94/18318; and in references cited herein.

[0803] In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, Nature 340:245-246; Chien et al., 1991, Proc. Natl. Acad. Sci. USA 88:9578-9582) can be used to identify molecules that specifically bind to connective tissue antigen polypeptides or connective tissue antigen-like polypeptides.

[0804] Where the connective tissue antigen binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

[0805] Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occurs every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

[0806] As mentioned above, in the case of a connective tissue antigen binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a connective tissue antigen binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

[0807] The selected connective tissue antigen binding polypeptide can be obtained by chemical synthesis or recombinant expression.

Other Activities

- [0808] A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.
- [0809] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.
- [0810] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte growth; therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.
- [0811] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be also employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.
- [0812] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.
- [0813] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the

present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

[0814] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

[0815] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

[0816] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

[0817] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

[0818] The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

Other Preferred Embodiments

[0819] Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ

ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 4 of Table 1A or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in Clone ID NO:Z.

[0820] Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of the portion of SEQ ID NO:X as defined in column 4, "ORF (From-To)", in Table 1A.

[0821] Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of the portion of SEQ ID NO:X as defined in columns 8 and 9, "NT From" and "NT To" respectively, in Table 2.

[0822] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 4 of Table 1A or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in Clone ID NO:Z.

[0823] Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the nucleotide sequence as defined in column 4 of Table 1A or columns 8 and 9 of Table 2 or the complementary strand thereto, and/or cDNA contained in Clone ID NO:Z.

[0824] A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of the portion of SEQ ID NO:X defined in column 4, "ORF (From-To)", in Table 1A.

[0825] A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of the portion of SEQ ID NO:X defined in columns 8 and 9, "NT From" and "NT To", respectively, in Table 2.

[0826] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, the